Faculdade de Medicina da Universidade de Lisboa

Original Thesis

Master in Metabolic Diseases and Eating Disorders

Predictors of Early Readmission in Chronic Heart Failure

REFERENCE

(p**RE**dictors o**F** **E**arly **RE**admission i**N** **C**hronic h**E**art failure)

Mário Augusto Rodrigues Teixeira Barbosa, MD

Coordinator: Luiz Filipe Menezes Falcão, MD, PhD

2018

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Dissertação elaborada para obtenção do grau de Mestre em Doenças Metabólicas e Comportamento Alimentar

2018

A impressão desta dissertação foi aprovada pelo Conselho Científico da Faculdade de Medicina de Lisboa em reunião de 19 de Fevereiro de 2019

Ser Médico é deixar de pertencer a ti próprio,
deixar de pertencer aos teus amigos,
à tua família e passar a pertencer
à grande família…
a Humanidade.

Mário Barbosa

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1. SUMMARY

The present thesis is based on the premise that chronic heart failure patients have a high morbidity and mortality due to the fact that cardiac insufficiency *per se* evolves inexorably, and that it affects an elder and frail population, suffering from multiple pathologies, polymedicated and even socio-economically vulnerable.

The increase of life expectancy, inherent to the improvement of health care, determined a parallel augment of chronic heart failure patients.

Albeit we have assisted to a consistent decline in the rate of heart failure hospitalizations, surprisingly, short-term readmission and mortality persist high, irrespective of clinical innovations and guideline directed management, representing a tremendous health care burden.

It urges to define a short-term prognosis for these patients in order to reduce the readmission and premature mortality rates due to its socio-economic impact.

The main purpose of this dissertation is to characterize at risk patients for early (defined as a period of 90 days post-discharge) readmission, due to heart failure, and overall death.

The putative role of biochemical cardiovascular markers in clinical decision making, principally in recognizing high risk patients that could benefit from therapeutic intensification and stricter surveillance is also addressed.

To characterize the population we addressed disease related risk factors [namely the etiology, the New York Heart Association Functional (NYHA) Class, left ventricular ejection fraction (LVEF), right ventricular function, signs and symptoms], non-modifiable cardiovascular risk factors, modifiable cardiovascular risk factors, comorbidities [chronic kidney disease (CKD), anemia, iron deficiency, thyroid function], therapeutic and biomarkers [specifically troponins, proBNP-Aminoterminal B-type Natriuretic Peptide (NT-proBNP), Galectin-3 (Gal-3), Suppression of Tumorigenicity 2 (ST2), Mid-Regional pro-Adrenomedullin (pro-ADM)] and Erythropoietin (EPO).

Key words:

Chronic heart failure; Short-term readmission; Short-term mortality; Galectin-3; ST2.

2. RESUMO

A presente tese baseia-se na premissa de que os doentes que padecem de insuficiência cardíaca crónica apresentam uma morbilidade e mortalidade elevadas fruto da evolução *per se* inexorável da insuficiência cardíaca e do facto de afetar uma população maioritariamente idosa, frágil, que sofre de múltiplas patologias, polimedicada e, inclusive, socioeconomicamente desprovida.

O aumento da esperança de vida, inerente à melhoria dos cuidados de saúde, determinou um incremento paralelo da prevalência da insuficiência cardíaca crónica.

Apesar de se ter assistido a um declínio das taxas de internamento por insuficiência cardíaca, surpreendentemente, as taxas de reinternamento e mortalidade precoces mantêm-se elevadas, independentemente dos avanços clínicos e abordagem em conformidade com as directrizes preconizadas, sobrecarregando tremendamente o sistema de saúde.

Atendendo ao seu impacto socioeconómico urge definir o prognóstico a curto prazo destes doentes a fim de reduzir a taxa de readmissão e mortalidade precoces.

Trata-se de um estudo de coorte prospetivo observacional, unicêntrico, com um único braço, de utilidade diagnóstica.

O objetivo principal do estudo foi caracterizar os doentes de risco para readmissão e mortalidade precoces (definido como o período até 90 dias pós-alta) por insuficiência cardíaca.

Apesar do propósito deste estudo ser, primeiramente, definir o prognóstico a curto prazo da insuficiência cardíaca, o seguimento prolongado permitiu-nos caracterizar, também, a mortalidade a longo prazo.

Consideramos a mortalidade global atendendo a que a maioria dos doentes não faleceu no hospital, pelo que não tivemos acesso às certidões de óbito.

O objetivo secundário foi avaliar a importância de biomarcadores emergentes no prognóstico da insuficiência cardíaca.

Para caracterizar a população abordamos fatores de risco relacionados com a insuficiência cardíaca *per se* (nomeadamente a etiologia, a classe funcional da NYHA, a fração de ejecção do ventrículo esquerdo, a função do ventrículo direito, sinais e sintomas), fatores de risco cardiovasculares não-modificáveis, factores de risco cardiovasculares modificáveis, comorbilidades (tais como a doença renal crónica, a anemia, a deficiência de ferro, a função tiroideia), a terapêutica e biomarcadores (troponinas, NT-proBNP, galectina-3, ST2, pro-ADM e EPO).

Os critérios de inclusão foram:

- admissão por insuficiência cardíaca classe III ou IV de NYHA;
- idade igual ou superior a 18 anos.

Os critérios de exclusão foram:

- óbito no primeiro internamento;
- alta contra-parecer médico;
- doença renal crónica com uma taxa de filtração glomerular <30 ml/min/1.73 m^2 [calculada através da fórmula Modification of Diet in Renal Disease (MDRD)] ou sob técnica de substituição renal;
- doença hepática moderada a grave;
- neoplasia ativa com ou sem metástases.

Foram recrutados 70 doentes dos quais 5 foram excluídos por lhes ter sido diagnosticado neoplasia ativa.

O recrutamento teve a duração de 12 meses, começando (primeiro participante) a 19/11/2015.

Os participantes foram seguidos até 30/09/2017 ou até à data de óbito.

Todos os participantes assinaram um consentimento informado.

Os métodos estatísticos utilizados foram:

Análise Descritiva:

As varáveis contínuas foram sumarizadas por média, mediana, desvio padrão, 1º e 3º quartis, intervalo interquartil e mínimo/máximo.

A comparação entre pacientes foi realizada para todas as variáveis utilizando o t test ou o Wilcoxon Rank test conforme aplicável.

As variáveis categóricas foram sumarizadas por frequências relativas e absolutas, e comparadas mediante o teste qui quadrado ou o teste exacto de Fisher, conforme aplicável.

Consideraram-se como variáveis de estratificação:

- a readmissão precoce;
- a mortalidade precoce;
- mortalidade a longo prazo.

Utilizou-se o Shapiro-Wilk test para avaliar a normalidade das variáveis contínuas.

Análises de Objetivos Primários:

Para se avaliar os objetivos primários deste estudo, efectuou-se uma análise de sobrevivência para cada um dos pontos de interesse (i.e. readmissão precoce, mortalidade precoce e mortalidade a longo prazo), utilizando curvas de sobrevivência de Kaplan Meier.

Aplicou-se o teste Log rank para comparar probabilidades de sobrevivência para cada uma das referidas variáveis.

Um modelo univariável de Cox (proporcionalidade das funções de risco) foi usado para se obter Hazard Ratios (HR) e intervalos de confiança de 95% para cada variável.

Utilizaram-se os resíduos de Schoenfeld para testar os hazards proporcionais.

Todas as análises foram conduzidas com um nível de significância global de 5%.

Não se efetuou imputação de dados em falta.

Não se fizeram ajustes para multiplicidade.

Toda a análise estatística foi realizada com o programa R Statistical Software version 3.4.3.

Atendendo a que alguns dos biomarcadores estudados não têm *cut-offs* definidos utilizou-se a Area Under the Curve Receiver-Operator Characteristic (AUCROC) conforme definida por Hand e Till.

O *cut-off* adequado para cada biomarcador foi definido usando o Índice de Youden.

Da análise estatística concluiu-se que o seguimento mediano foi de 13.7 (6.7-18.9) meses.

A idade média da população estudada foi 79.2 ±10.8 anos.

A amostra foi constituída maioritariamente por participantes do sexo feminino (56.9%).

Salientamos que a fração de ejecção média foi de 50.38 ± 19.07 %.

A taxa de readmissão aos 30 dias pós-alta foi de 15.4% e aos 90 dias de 33.8%, em sintonia com dados nacionais.

A mortalidade aos 30 dias pós-alta foi de 10.8% e aos 90 dias de 18.5%, também de acordo com a literatura.

Destacamos que a mortalidade anual foi de 36.9% e no fim do seguimento [mediana 13.7 (6.7-18.9) meses] 40% dos participantes tinha perecido.

Estes dados espelham a gravidade clínica dos doentes que padecem de insuficiência cardíaca.

O internamento médio foi de 8.3 dias, o que, também, reflecte a complexidade dos casos abordados.

Os doentes com vários internamentos, com maior número de dias de internamento acumulado e com internamentos prolongados tiveram pior prognóstico.

De acordo com os resultados obtidos, o doente de risco para readmissão e morte no período crítico dos 90 dias após alta, é idoso e sofre de várias comorbilidades, nomeadamente doenças metabólicas.

Curiosamente, a obesidade correlacionou-se com um melhor prognóstico.

Das várias comorbilidades de que padecem os doentes com insuficiência cardíaca, verificamos que a insuficiência renal se correlacionou com todos os objetivos primários visados.

Salientamos que a síndrome cardiorenal tipo 1 determinou um risco acrescido de mortalidade precoce e a longo prazo.

A anemia e a ferropenia absoluta condicionaram o prognóstico, sendo que valores elevados do estimulador da hematopoiese, eritropoeitina, se correlacionaram com a mortalidade precoce e a longo prazo.

O índice de dispersão eritrocitário, frequentemente negligenciado na estratificação do risco do doente com insuficiência cardíaca, apresentou-se como um interessante preditor de mau prognóstico para a readmissão e mortalidade precoces e para a mortalidade tardia.

A fracção de ejecção do ventrículo esquerdo revelou-se um preditor de mortalidade a longo prazo nos doentes com fracção de ejeção reduzida, e apresentou uma tendência para a readmissão e mortalidade precoces no mesmo subgrupo.

A avaliação de elementos ecocardiográficos (pressão sistólica da artéria pulmonar, excursão sistólica do plano do anel tricúspide e ausência de colapso da veia cava inferior) permitiu a identificação de uma relação entre disfunção sistólica do ventrículo direito e pior prognóstico.

Estes dados corroboram a impressão que apesar da importância lapidar da função do ventrículo esquerdo, a avaliação da função ventricular direita acrescenta informação valiosa para a estratificação do risco dos doentes com insuficiência cardíaca.

Potenciais causas de hipoperfusão, tais como a hipotensão sistólica e diastólica foram marcadores de mau prognóstico para mortalidade precoce e a longo prazo.

O péptido natriurético NT-proBNP, apontado na literatura, essencialmente, como adjuvante no diagnóstico, destacou-se como um preditor fidedigno de mortalidade precoce e a longo prazo, por correlação positiva.

A troponina ultra-sensível (hsTnT) revelou-se um preditor de mortalidade a longo prazo, por correlação positiva, e quando associada a valores elevados de NT-proBNP agravou o risco de readmissão precoce.

Ressalvamos que os biomarcadores supracitados, quando avaliados por separado não se correlacionaram com a readmissão precoce, mas a aferição conjunta ditou um risco acrescido desse objetivo primário.

A Gal-3 foi um marcador de mau prognóstico para a readmissão e mortalidade precoces e para a mortalidade tardia.

Quanto ao ST2 foi um preditor de mortalidade a longo prazo.

Não se estabeleceu qualquer relação com significado estatístico com a pro-ADM, possivelmente pelo facto da amostra ser relativamente pequena.

Cremos que o nosso estudo poderá contribuir para a definição do doente de risco com insuficiência cardíaca no período crítico dos 90 dias após a alta clínica.

Palavras-chave:

Insuficiência cardíaca crónica; Readmissão precoce; Mortalidade precoce, Galectina-3; ST2.

3. ABBREVIATIONS AND ACRONYMS

ACC - American College of Cardiology

ACE - Angiotensin-Converting-Enzyme

ADHF - Acute Decompensated Heart Failure

ADQI - Acute Disease Quality Initiative

AF - Atrial Fibrillation

AHA - American Heart Association

ARB - Angiotensin Receptor Blocker

AUC - Area Under the Curve

BB - Beta Blocker

BMI - Body Mass Index

BNP - B-type natriuretic peptide

CHF - Chronic Heart Failure

CI - Confidence Interval

CKD - Chronic Kidney Disease

cTnI - Cardiac Troponin I

cTnT - Cardiac Troponin T

CV - Cardiovascular

EAS - European Atherosclerosis Society

ECG - 12-lead electrocardiogram

EDTA - Ethylenediaminetetraacetic Acid

ELISA - Enzyme-Linked Immunosorbent Assay

EPO - Erythropoietin

ESC - European Society of Cardiology

ESH - European Society of Hypertension

FT3 - Free Triiodothyronine

FT4 - Free Thyroxine

Gal-3 - Galectin-3

GFR - Glomerular Filtration Rate

HR - Hazard Ratio

HF - Heart Failure

HFSA - Heart Failure Society of America

HFmrEF - Heart Failure with Mid-Range Ejection Fraction

HFpEF - Heart Failure with Preserved Ejection Fraction

HFrEF - Heart Failure with Reduced Ejection Fraction

hsTnT - Highly Sensitive Troponin T

IDF - International Diabetes Federation

IL - Interleukin

LBBB - Left Bundle Branch Block

LV - Left Ventricular

LVEF - Left Ventricular Ejection Fraction

MR-proADM - Mid-Regional pro-Adrenomedullin

MRA - Mineralocorticoid Receptor Antagonist

NPV- Negative Predictive Value

NT - proBNP- Aminoterminal B-type Natriuretic Peptide

NYHA - New York Heart Association

PASP - Pulmonary Artery Systolic Pressure

PPV - Positive Predictive Value

RBBB - Right Bundle Branch Block

RDW - Red Cell Distribution Width

ROC - Receiver-Operator Characteristic

SD - Standard Deviation

ST2 - Suppression of Tumorigenicity 2

TAPSE - tricuspid annulus plane systolic excursion

TSH - Thyroid Stimulating Hormone

USA - United States of America

WHO - World Health Organization

4. INTRODUCTION

The current European guidelines define heart failure (HF) as an alteration of the cardiac structure or function resulting in a deficient oxygen intake to the tissues, despite adequate filling pressures (or solely at expenses of high filling pressures), which is clinically characterized by a constellation of symptoms and typical signs.[1]

It is estimated that around 15 million europeans[2] and 6 million americans[3] suffer from chronic heart failure (CHF), moreover the prevalence is superior to 10% in the population over 70 years of age.[4]

Although we have witnessed a decrease in hospitalization due to CHF of about 30.5% in the last decade, the rehospitalization rate dropped just 9.7% in the same time period.[5,6]

Up to 25% of patients with HF are readmitted in the first 30 days after hospital discharge[7,8] and approximately 30% are readmitted 60 to 90 days post-discharge[9,10] despite management consentaneous with the preconized guidelines and evidence based, diagnostic advances, innovative drugs and new therapeutic devices.

Adding to this matter is the mortality rate 60 to 90 day post-discharge of about 15%.[8]

Decompensated HF requiring hospitalization is a serious condition which progresses with high mortality and high readmission rates.

Strikingly, the 10-year mortality for patients newly admitted with HF is estimated to be around 100%.[11]

Due to its poor outcome, HF could be considered a "malignant condition".[12]

Patients with HF are mostly elderly, with multiple comorbidities, namely metabolic diseases, and are polymedicated, showing a readmission and mortality rate at 90 days of discharge, respectively 8 and 11 times higher than the general population.[13]

Most of these diseases are both the *primum movens* and independent risk factors, as HF etiology determines its prognosis.

According to the Prevalence of Chronic Heart Failure in Southwestern Europe (EPICA) trial, the estimated prevalence of CHF, in Portugal, between the ages of 20 and 50 is 1.36%, peaking to 16% in the population older than 80 years.[14,15]

The EPICA investigators also found that two-thirds of HF patients are hospitalized, in average, twice in a year and that 20 to 30% are readmitted within three months of hospital discharge.[14,15]

Given the complexity and prevalence of the HF syndrome, it is mandatory to discriminate high risk patients that can benefit from a thorough assessment and define effective diagnosis and prognosis strategies.

Early readmissions are mainly related with volume overload, while later rehospitalizations are the consequence of the inexorable progression of this syndrome, which is inherently linked to cardiac remodeling. [16]

Ergo, the first three months post-discharge are crucial in HF's evolution, and since the short-term prognosis has failed to improve over the past decade despite updated management, one should intervene assertively in this golden period.

The novel biochemical markers emerge as promising tools that can complement traditional clinical practice.

5. FUNDAMENTALS

A policy statement from the American Heart Association (AHA) underlines that the number of HF patients is expected to duplicate until 2030 and consequently its social impact.[17]

Hospitalization for HF represents a major burden on healthcare services worldwide, and is a strong predictor of increased mortality, particularly, in the first months post-discharge.[18]

Heart failure is the leading cause of admission in Europe and in the United States of America (USA), accounting for 1 to 2% of all hospitalizations.[16]

Furthermore, around 30% of these patients require rehospitalization within 60 to 90 days.[19]

The National Heart Failure Audit of almost 57 000 hospitalizations in England and Wales, from 2014 to 2015, showcased an in-hospital mortality of 9.6%, a 30-day mortality of nearly 20% and a mortality at one year of 30%. Unfortunately, the reported rates did not improve for the past six years.[20]

Despite the socio-economic relevance that the characterization and acknowledgement of rehospitalizations due to HF may yield, national trials focusing this topic are scant, thus this study could render a little contribution to this matter.

The EPICA trial, dating from 2002, is the only Portuguese HF prevalence study, so, given the substantial social, economic and cultural changes in our country in the past two decades it is crucial to understand the new trends of this overwhelming syndrome.

The Portuguese Consensus Statement for the improvement of HF, released in 2017, recognized that, regardless of HF prevalence, general population and politicians are not aware of its social importance.[21]

The EPICA study estimated a 4.36% HF global prevalence, varying from 1.36% between the ages of 25-49, to 16.14% in the population over 80 years of age.

However, the ageing of the population led to an inevitable increase in HF's prevalence, and based on the 2011 Portuguese Census, there is an estimated 380 000 HF patients in Portugal.[22]

Relying on recent Portuguese Health System official data, HF as the primary diagnosis represents the second highest hospital burden, being responsible for 182 512 hospitalization days corresponding to 18 588 patients, with a mean hospital stay of 9.8 days and an in-hospital mortality of 12.5%.[23]

Still, these numbers are underestimated as HF is often neglected when classified as a secondary diagnosis.[24]

From 2004 to 2012 the number of HF admissions in Portugal increased 33% and the readmission rate, especially at 30 (14.6%) and 60 days, also rose.[25]

Twenty years ago HF hospitalizations in Portugal represented a sum of around 24 million euros, nowadays the economic impact is surely higher given its increasing prevalence and prolongation of HF patients' survival.[26]

5.1. THE IMPACT OF CHRONIC HEART FAILURE READMISSIONS

The increase in life expectancy generated what probably is the greatest challenge in modern medicine: to prolong the quantity of life while preserving the quality of life.[27]

The evolution towards chronicity of the most prevalent illnesses in the western world, and the consistent increase of survival in patients with chronical illnesses implies, inevitably, an enhanced hazard of readmissions due to acute decompensation.

Ageing of the population due to the prolongation of life span of patients with chronic conditions, inherent to the improvement in health care, has led to an increase in the prevalence of HF, making this disease a major and growing public health problem.

According to the latest European guidelines, HF has an estimated prevalence of 1 to 2% in the adult population. The percentage of HF patients increases with age, affecting at least 10% of the individuals aged 70 years or older.[1]

The acute pathologies, with emphasis towards infectious diseases, exacerbation of comorbidities, non-compliance to evidence-based therapies, clinical inertia/ patient under-treatment, complications associated to treatment, the inevitable evolution of some chronic diseases, the clinical and socio-economical fragility of the more advanced age groups, represent the main causes of chronic disease decompensation.

Acknowledging the precipitants of chronic illnesses decompensation, describing risk factors correlated to hospital readmission is fundamental.

Hospital readmission entails an expenditure of resources, being considered a quality parameter of the provided healthcare.[28]

High readmission rates translate into an increase in hospital expenses, a decline in provided care quality and are related to high hospital mortality percentages.[29]

In-hospital mortality rates are greater in readmitted patients, given the fact that readmissions often represent more severe clinical scenarios.[30]

The definition of hospital readmission is not consensual, determining great disparity among series (the percentage of readmissions in the USA for adult individuals varies between 5% and 29%).[30]

Readmission is defined as a new hospitalization occurring in a period of 1, 2, 4 or 12 months after discharge.[31]

Regardless of the generalized use of the readmission rate to ascertain the quality of healthcare, there is evidence that maybe it is not a reliable evaluation criterion.[32]

Such occurs due to the multiplicity of conditionings that envelop readmission.

Apart from patient characteristics, such as age, gender, comorbidities,[29] hospital characteristics affect as well the readmission rate.[33]

Ansari et al., divulged that central hospitals have a higher readmission rate, since by being more specialized, receive more complex patients and with higher clinical severity, hence more prone to being readmitted.[34]

Kossovsky et al., disclosed that HF readmissions would be more related to the clinical and demographics characteristics rather than hospital care quality.[35]

A study addressing the same issue did not find a correlation between this parameter and hospital provided care.[36]

The understanding of the determining factors for rehospitalizations may contribute to outline strategies capable of reducing readmissions and consequently the costs related to healthcare.[37]

The identification of hospital readmission risk factors may improve, as well, the performance of healthcare practitioners and therefore the prognosis of chronic patients.

5.2. THE IMPORTANCE OF BIOMARKERS

Clinical judgement, the cornerstone of medical *praxis* is enhanced by imaging and biological diagnostic tests.

Eugene Braunwald, a decade ago, produced a meticulous review addressing the increasing importance of biomarkers in the management of HF, anticipating a multi-marker strategy for HF risk stratification.[38]

Since then, scientific advance has brought us several physiopathological biomarkers of HF.

Despite its undisputed utility, most of these biomarkers are expensive and are not available in most laboratories which limit its application in a daily basis.

Besides, some lack a well-consolidated threshold.

Multiple cardiovascular disorders provoke myocyte sustained injury leading to cardiac remodeling which stimulates proliferation of interstitial fibroblasts and biosynthesis of extracellular matrix components, culminating in cardiac fibrosis.

Beyond its diagnostic, prognostic and, eventual, therapeutic monitoring use, many researchers have explored its value in the inhibition of cardiac remodeling, raising the possibility of novel therapeutic targets.

The overwhelming amount of data exploring this topic favors natriuretic peptides as the most reliable diagnostic predictors.

Nonetheless, promising novel biomarkers, namely galectin-3, mid-regional pro-adrenomedullin and ST2 seem to be superior to the traditional natriuretic peptides concerning prognosis.

Furthermore, a multi-marker strategy appears to yield additional information, as current data alludes a synergism between natriuretic peptides and the cited biomarkers.

Biologic markers allow quantification of certain physiopathological processes.[39]

Ideally, a marker should fulfill the following criteria: accuracy warranting a precise identification of at risk subjects; reliability which represents the ability of reproducing consistently the results; and therapeutic importance with early intervention.[40]

The vast consistent data addressing emerging cardiac fibrosis markers as adjunctive to conventional clinical risk factors and natriuretic peptides dosing, led the American College of Cardiology (ACC)/ American Heart Association to grant ST2 and Gal-3 evaluation a class II recommendation for CHF prognosis, in 2013.[41]

Heart failure management through biological markers is based on the assumption that variations over time reflect clinical improvement or disease progression. Yet, translating analytical data to clinical practice is complex.[42]

When it comes to biomarker interpretation two variables should be taken into account: the analytical variability (inaccuracy of the test) and the biological variability (anticipated variability within a person over time).[43]

6. METHODS

6.1. STUDY POPULATION

6.1.1. RECRUITMENT, ENROLLMENT PERIOD, AND SAMPLE SIZE

The study was conducted in the Department I of Internal Medicine of the Santa Maria University Hospital, with the approval of the Academic Medical Center Ethics Committee. (Attachment I)
The study enrolled 70 patients admitted to ward with acute heart failure NYHA class III and IV, recruited over a planned recruitment period of 12 months, starting (first subject) on 19/11/2015.
Ages eligible for study: 18 years and older.
Genders eligible for study: both.
All patients enrolled were followed until 30/09/2017 or date of death (whichever occurred first).

6.1.2. INCLUSION CRITERIA

Patients admitted with acute decompensated heart failure in class III or IV of NYHA.
Written informed consent was requested to all eligible patients. (Attachment II)

6.1.3. EXCLUSION CRITERIA

- in-hospital death in the first hospitalization;
- hospital discharge against medical advice;
- chronic kidney disease patients with a glomerular filtration rate (GFR) <30 ml/min/1.73 m^2 (calculated with the MDRD score) or under kidney substitution technique;
- moderate or severe hepatic impairment (calculated with the Child-Pugh score);
- active neoplasm with or without metastasis.

6.2. STUDY DESIGN

6.2.1. STUDY DESIGN

Observational prospective cohort, single-center, single-arm, diagnostic utility study.

6.2.2. ENDPOINTS

Primary endpoints:
Characterize at risk patients for early readmission due to heart failure (defined as readmission up to 90 days post-discharge) and for short-term mortality (defined as death occurred within 90 days post-discharge).

We considered all-cause mortality given that most of the patients did not die in the hospital and, therefore, we did not have access to the death certificates.

Secondary endpoints:
Assess the importance of new cardiovascular risk biomarkers (such as Gal-3, ST2, Pro-ADM and EPO) in the prognosis of cardiac insufficiency namely early readmission due to heart failure, overall short-term mortality and overall long-term mortality.

Although the purpose of this study was primarily to define short-term heart failure outcome, the extended follow-up allowed us to characterize long-term mortality.

6.3. STUDY PROCEDURE

6.3.1. STUDY PATIENTS

The study encompassed patients admitted to ward with acute decompensated heart failure NYHA class III and IV.
Patient assessment was based on a protocol that included clinical history, physical examination, 12-lead electrocardiogram (ECG), thoracic X-ray, blood sampling for laboratory tests, transthoracic Doppler echocardiography and therapeutic data. (Attachment III)

6.3.2. MASKING

The author was blinded for the measurements of the biomarkers since the results were only acknowledged at study completion.
It is an observational study as there was no interference in clinical decisions.
Protocol´s laboratory tests, ECG, thoracic X-ray and transthoracic Doppler echocardiography were performed as per routine clinical practice.

6.3.3. EXAMS

A postero-anterior chest X-ray was performed with a conventional equipment to the studied population.
A 12 lead ECG was executed using a 3 channel conventional equipment, and its interpretation was based on the American Heart Association Electrocardiography and Arrhythmias Committee criteria (vide Protocol).
All echocardiograms M mode, two-dimensional and Doppler were performed by an experienced operator.

Using a Hitachi Aloka alfa 6 Medical device with a 2.5 MHz transducer, an echocardiographic examination was made with the subject lying in the left lateral recumbent position. The parasternal long and short axis, and the apical four- and two-chamber views were observed.

Aortic, tricuspid and pulmonary transvalvular flows were also collected.

The segmental contractility was obtained using a 16 segments model and echocardiographic values were determined in accordance with the American Society of Echocardiography (vide Protocol).

Left ventricular (LV) volumes were calculated by the biplane Simpson method, performing manual planimetry of the left ventricle endocardial contour area, at the insertion of the mitral valve cusps to the apex, in systole and diastole.

Diastolic function evaluation was estimated through the observation of mitral transvalvular curves, based on E and A wave velocity and deceleration time; tissue Doppler was applied to record mitral annular velocities at the septal and lateral sides of the annulus. E/E`ratio was determined. Left atrial maximal volume index was calculated.

Pulmonary artery systolic pressure (PASP) was quantified through tricuspid regurgitant flow.

A subcostal evaluation of the inferior vena cava was also performed.

6.3.4. BLOOD SAMPLES

Biomarkers were measured using plasma samples.

Plasma samples were stored at the study sites at -20ºC, followed by storage at -80ºC.

Galectin-3, ST2/IL-33R, mid-regional pro-adrenomedullin and erythropoietin were quantified in plasma using pre-coated human ELISA kits (galectin-3, ST2/ Interleukin (IL)-33R and erythropoietin with R&D Systems, Abingdon, USA and mid-regional pro-adrenomedullin with Elabscience Biotechnology Co., Ltd).

The reference range for galectin-3, ST2/IL-33R, mid-regional pro-adrenomedullin and erythropoietin were 0.3-10 ng/mL, 31.3-2000 pg/mL, 15.625-1000 pg/mL and 2.5-200 mIU/mL, respectively; and the minimum detectable amounts was 0.085 ng/mL, 13.5 pg/mL, 9.375 pg/mL and 0.6 mIU/mL, respectively.

Plasma hsTnT levels were measured by electrochemiluminescence immunoassay Elecsys Troponin T high sensitive (limit of detection: 5 ng/L), Roche Diagnostics, GmbH, Mannheim, Germany.

Plasma NT-proBNP values were measured using electrochemiluminescence immunoassay Elecsys NT-proBNP (measuring range: 5-35,000 ng/L) Roche Diagnostics, GmbH, Mannheim, Germany.

Biochemical parameters related to Cardiac Troponin I (cTnI), renal, hepatic and thyroid function, ionogram and iron kinetics were evaluated using the same plasma sample.

Haematological values were determined using Ethylenediaminetetraacetic Acid (EDTA) whole blood.

6.4. DATA COLLECTION INSTRUMENTS

Data was collected in an Excel database.

6.5. STATISTICAL METHODS

6.5.1. STUDY ENDPOINTS

This study has 3 primary endpoints directly associated with each of the primary objectives as presented and defined below:

Endpoint	Baseline	Censoring
Early Readmission Definition Patient rehospitalization less than 90 days after a hospitalization discharge.	First observation (hospitalization) of each patient in which an early rehospitalization occurred after discharge (i.e. the patient was rehospitalized less than 90 days afterwards). For subjects without early rehospitalization events, the baseline (first observation) was considered. It was also decided to consider the baseline data for subjects who did not have any early rehospitalization event after the baseline, but for whom the baseline was an early rehospitalization itself. In those cases, the subject was considered as having the event, and the time to event (used during survival analysis) was calculated based on the last hospitalization dates.	For subjects not having an early readmission event, censoring criteria was defined as 90 days.
Early Mortality Definition Patient died less than 90 days after a hospitalization discharge.	Last observation (hospitalization) of each patient before the early mortality event took place. For subjects that did not suffer early death event, the baseline (first observation) was considered.	For subjects not having early mortality event, censoring criteria was defined as 90 days.
Long-term Mortality Definition Patient died during follow-up.	Baseline (first observation) was considered for all patients.	For subjects alive by the end of the study, censoring criteria was defined as “End of study” date (30/09/2017).

Table 1 - Primary endpoints

6.5.2. GENERAL STATISTICAL METHODS

6.5.2.1. Descriptive Analysis

Unless specified otherwise, continuous variables were summarized by mean, standard deviation (SD), median, 1st and 3rd quartiles, interquartile range and minimum/maximum. Comparison between patients with and without each of the events was performed for all variables using t test or Wilcoxon Rank test as applicable. Categorical variables were summarized by relative and absolute frequencies, and compared using chi-squared test or Fisher's Exact test as applicable.

The following were considered as stratification variables for:

- Early readmission;
- Early mortality;
- Long term mortality

Shapiro-Wilk test was used to assess the normality of continuous variables.

6.5.2.2. Analysis of Primary Endpoints

For the analysis of the primary endpoints of this study, a survival analysis was performed for each of the 3 events of interest (i.e. early rehospitalization, early mortality and long-term mortality). For each endpoint, Kaplan Meier survival estimates were calculated and plotted for each categorical variable. Log rank test was used to compare survival probabilities in each of the considered variables. A univariate Cox proportional hazards model was fitted to the data to obtain HR and 95% confidence intervals for each variable. The proportional hazards assumption was tested using Schoenfeld residuals.

All analyses were conducted at an overall significance level of 5%. No imputation was performed on missing data. No adjustment for multiplicity was performed.

All statistical analyses were conducted using R Statistical Software version 3.4.3.

6.5.3. BIOMARKERS' CUT-OFF

To be able to analyse the prognosis capabilities of each biomarker and using multiple biomarkers at the same time, specific cut-offs for each of them were needed. Since there are no standardized cut-offs defined for most of these biomarkers, the multiclass AUCROC as defined by Hand and Till was used to assess the overall performance of each biomarker as a predictor of each of the events of interest (i.e. early rehospitalization, early mortality and long-term mortality). Due to the low number of subjects, to be able to

calculate some viable cut-offs, it was decided to use cut-offs calculated for biomarkers with AUCROC above 0.7 and 95% confidence intervals (CI) significantly different from 0.5 (i.e. not containing 0.5).
The optimal cut-off value for each biomarker to predict each of the events was defined using the Youden Index, which maximizes the sensitivity and specificity of the predictor. Negative predictive values (NPV) and positive predictive values (PPV) were calculated and reported for the selected cut-offs.

6.6. COMPLIANCE STATEMENTS

6.6.1. GENERAL REQUIREMENTS

The study was performed in conformity with its protocol, the Declaration of Helsinki and the Oviedo Convention. The study was approved by the Faculty of Medicine of the University of Lisbon Academic Medical Center Ethics Committee.

6.6.2. SUBJECT INFORMATION AND INFORMED CONSENT

Subjects or legal surrogates were informed orally and in written about the purposes of the study, study procedures and potential risks.
Before any study-related activities were initiated, the subjects or legal proxies signed the written informed consent.
The participation in the study was entirely voluntary.
The subjects have the right to withdraw their willingness to participate in the study at any time without affecting their future medical care in any way.

6.6.3. CLINICAL STUDY RESULTS AND PUBLICATION

The results of the study are documented in the present dissertation and, if possible, will be published (e.g. in scientific journals and/or presented in scientific meetings).

6.6.4. DATA CONFIDENTIALITY AND DATA PROTECTION

Auditors, Ethics Committee, and the regulatory authorities will be granted access to the subjects' medical records to the extent permitted by the applicable law and regulation for verification of clinical study procedures, and/or data control, ensuring subject data confidentiality.
The participants' file and the source data will be archived in line with national and international legal requirements.

7. DEFINITIONS

Arterial Hypertension was defined according to the European Society of Hypertension (ESH)/ European Society of Cardiology (ESC) Guidelines and/or taking hypertensive medication).[44]

Diabetes was defined following the International Diabetes Federation (IDF) criteria and/or use of antidiabetic drugs.[45]

Dyslipidemia was defined in accordance with the European Atherosclerosis Society (EAS) and the ESC Guidelines and/or use of lipid-lowering medication.[46]

Obesity was defined as body mass index (BMI) ≥30 kg/m^2 (calculated as weight divided by height squared)].[47]

Tabagism was defined as having ever smoked at least 100 cigarettes in the lifetime.[48]

Glomerular filtration rate was estimated using the MDRD formula.[49]

Cardiorenal syndrome type I was defined as an acute worsening of cardiac function leading to acute kidney injury (defined by an increase in serum creatinine of ≥0.3 mg/dL) in accordance to the 7th Acute Disease Quality Initiative (ADQI) Consensus Conference. [50]

Anemia was defined according to the World Health Organization (WHO) as hemoglobin <13 g/dL in men and <12 g/dL in women.[51]

Iron deficiency associated to CHF is defined, by the ESC and the AHA/ACC/ Heart Failure Society of America (HFSA), as absolute (when ferritin <100 µg/L) and as functional (if ferritin is between 100-300 µg/L with a transferrin saturation <20%).[1,52]

8. RESULTS

8.1. BASELINE CHARACTERISTICS

From the 70 selected patients 5 were excluded given that during follow-up they were diagnosed with active cancer.

Based on the study protocol over 200 variables were extracted and analyzed resulting in an overwhelming amount of data.

To facilitate the interpretation of the results only the population characteristics considered primordial are described (Table 1).

This study included 65 patients who matched the selection criteria and had a median follow-up period of 13.7 (6.7-18.9) months.

The **mean age** of the patients **was 79.2 ± 10.8 years**, **56.9% were female**, and their **mean Left Ventricular Ejection Fraction (LVEF) was 50.38 ± 19.07 %**.

8.1.1. READMISSIONS

From the 65 patients that full-filled inclusion criteria, **33.8% were rehospitalized within 90 days post-discharge**, **13.8% of which in the first 30 days after discharge**.

In our study **32.4% of women were readmitted precociously versus 35.7% of men**.

The **year readmission** percentage **was 61.5%**.

8.1.2. MORTALITY

The **30-day mortality prevalence was 10.8%** and the **90-day mortality prevalence was 18.5%**.

A trend towards compromised short-term survival and age ≥90 years was noted in the Heart Failure with Preserved Ejection Fraction (HFpEF) group (HR: 6.632, 95% CI: 0.599-73.409, P-value=0.123).

Short-term mortality was similar between genders (18.9% for the females versus 17.9% for the males) but men showed a greater percentage of long-term death (42.9% versus 37.8%). Nevertheless, none of these differences were statistically significant.

Figure 1 represents the Kaplan Meier long-term mortality curve between genders.

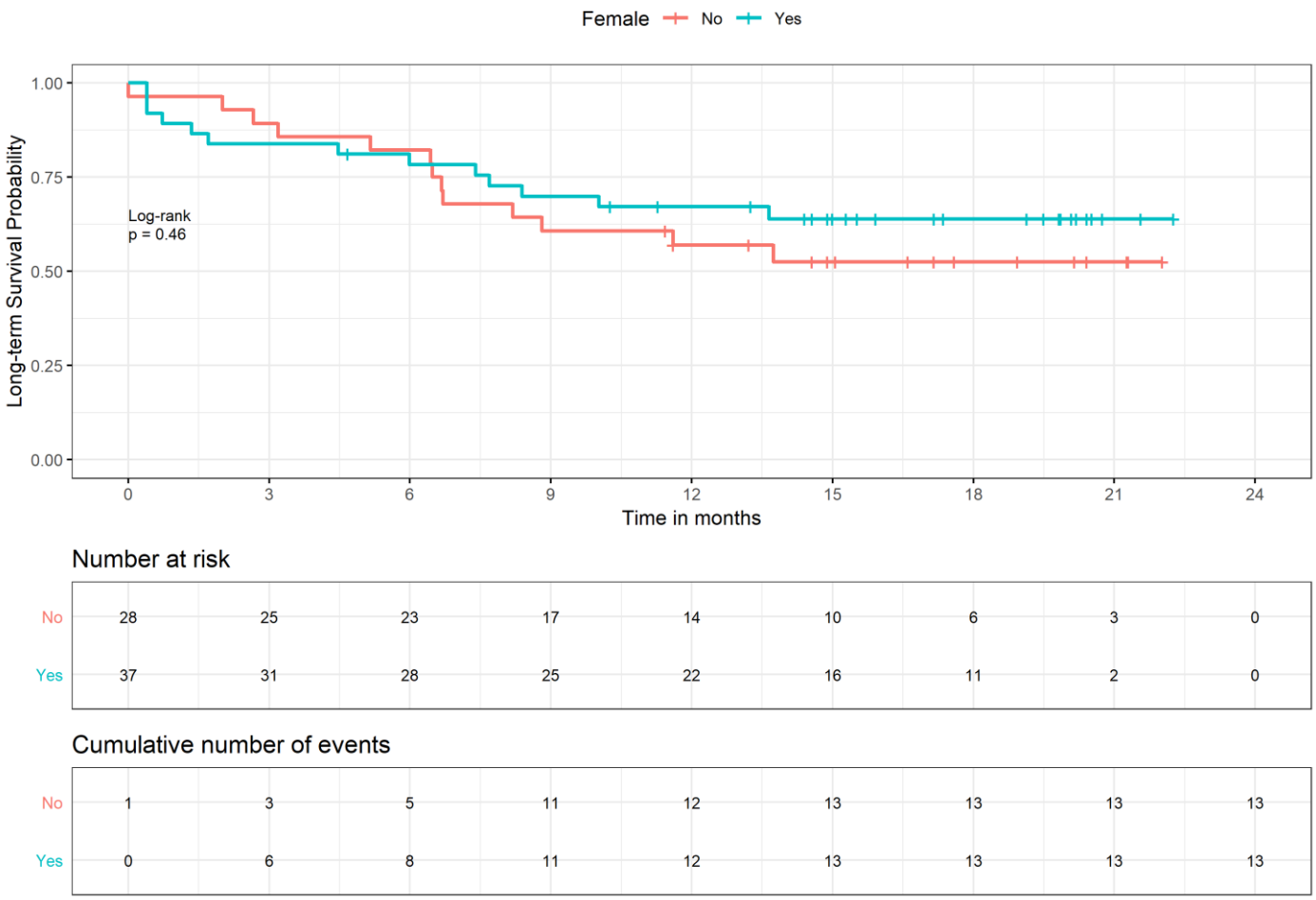

Figure 1 - Long-term mortality - Kaplan Meier: Gender

The **year mortality was 36.9%** and **40% of patients deceased at the end of follow-up**.

8.2. DISEASE RELATED DETERMINANTS

8.2.1. HOSPITALIZATIONS

The **accumulated length of stay represented a risk factor for short-term HF readmission** in the general population study (HR: 1.022, 95% CI: 1.009-1.036, P-value<0.001).

The **number of hospitalizations was related with short-term readmission in the general population** (HR: 1.543, 95% CI: 1.224-1.945, P- value<0.001) **and in the Heart Failure with Mid-Range Ejection Fraction (HFmrEF) subgroup** (HR: 2.814, 95% CI: 1.075-7.365, P- value=0.035) and expressed a trend towards greater risk in the HFpEF subgroup (HR: 1.391, 95% CI: 0.989-1.956, P- value=0.058).

In patients suffering from Heart Failure with Reduced Ejection Fraction (HFrEF) early readmission risk, derived from the **accumulated length of stay**, **was slightly superior to that of the general population** (HR: 1.029, 95% CI: 1.008-1.050, P-value=0.006).

For the same group a trend towards the length of stay for a given hospitalization and early readmission was met (HR: 1.173, 95% CI: 0.985-1.395, P-value=0.073) and another trend was found between the number of hospitalizations and early readmission (HR: 1.560, 95% CI: 0.997-2.442, P-value=0.052).

A trend towards the accumulated length of stay and short-term mortality, close to reaching statistical significance (HR: 1.016, 95% CI: 0.999-1.032, P value=0.062), was identified in the general population study.

A trend towards the accumulated length of stay and long-term mortality was identified in the general population study (HR: 1.009, 95% CI: 0.996-1.022, P value=0.170) and in the HFmrEF subgroup (HR: 0.882, 95% CI: 0.740-1.052, P value=0.162).

A trend towards the number of hospitalizations and long-term mortality close to reaching statistical significance (HR: 1.506, 95% CI: 0.994-2.283, P value=0.054) was found in the HFrEF subgroup.

In the HFpEF subgroup both the length of stay per specific admission (HR: 1.063, 95% CI: 1.006-1.123, P value=0.030) **and the accumulated length of stay** for all admissions (HR: 1.051, 95% CI: 1.008-1.095, P value=0.019) **were markers of worse long-term survival**.

8.2.2. ETIOLOGY

The main causes of HF (i.e. ischemic cardiomyopathy, hypertensive cardiomyopathy and valvular cardiomyopathy) were studied but only the first showed an interesting result, since that in the subgroup of patients with HFrEF ischemic cardiomyopathy increased the risk of early readmission close to 5 times with an almost statistical significance (HR: 4.648, 95% CI: 0.892-24.225, P-value=0.068) and a trend towards ischemic cardiomyopathy and long-term mortality was also recognized (HR: 3.321, 95% CI: 0.789-13.977, P-value=0.102).

8.2.3. LEFT VENTRICULAR EJECTION FRACTION

We verified a trend towards short-term readmission and LVEF in the HFrEF subgroup (HR: 0.516, 95% CI: 0.228-1.168, P-value=0.112).

A trend towards short-term survival and LVEF was also patent in the HFrEF subgroup (HR: 0.274, 95% CI: 0.053-1.422, P-value=0.123).

As for **long-term mortality**, statistical significance was met in the HFrEF subgroup, as **per increments of 10% of LVEF a risk reduction of 65.2% was found** (HR: 0.348, 95% CI: 0.135-0.899, P-value=0.029).

8.2.4. REDUCED RIGHT VENTRICULAR FUNCTION

We were able to identify a trend towards decreased TAPSE and long-term mortality (P-value=0.092). The mean TAPSE of the group of deceased patients was 17 mm.

A trend towards elevated PASP [median value in the group of patients who died of 45.00 (30.60-54.34 mmHg)] and long-term mortality was found as well (P-value=0.086).

Using descriptive analyses, we acknowledged that the **absence of inferior vena cava inspiratory collapse** was far **more frequent in the group that died during the first 90 days post-discharge** (33.3%) than in the survivor group (9.4%). The difference between the two groups was significant (P-value=0.015).

Regarding **long-term mortality**, the **absence of inferior vena cava inspiratory collapse** was observed in only 2.6% of the patients who survived compared to 30.8% of those who died during follow-up, with an also significant difference between groups (P-value<0.001).

8.2.5. OTHER ECHOCARDIOGRAPHIC FINDINGS

In our study **LV end-diastolic volume was a predictor of short-term mortality** (P-value=0.027).

The median LV end-diastolic volume value for the patients that survived was 56.87 (36.37-82.88) cm^3 whereas in the subset of patients who died before 90 days post-discharge the median value was 105.40 (85.25-150.00) cm^3.

Long- term mortality was also predicted by LV end-diastolic volume (P-value=0.023).

The median value for the patients that survived was 44.57 (34.79-76.44) cm^3 while in the subset of patients who died through follow-up the median value was 84.07 (58.83-151.00) cm^3.

8.2.6. REFRACTORY SIGNS OF CONGESTION

According to descriptive analyses, **hepatomegaly** was **observed in only 1.9% of the patients that survived the first 90 days post-discharge** versus 25% of those who deceased in that period.

The difference between the two groups was statistically significant (P-value=0.018), as represented in Figure 2.

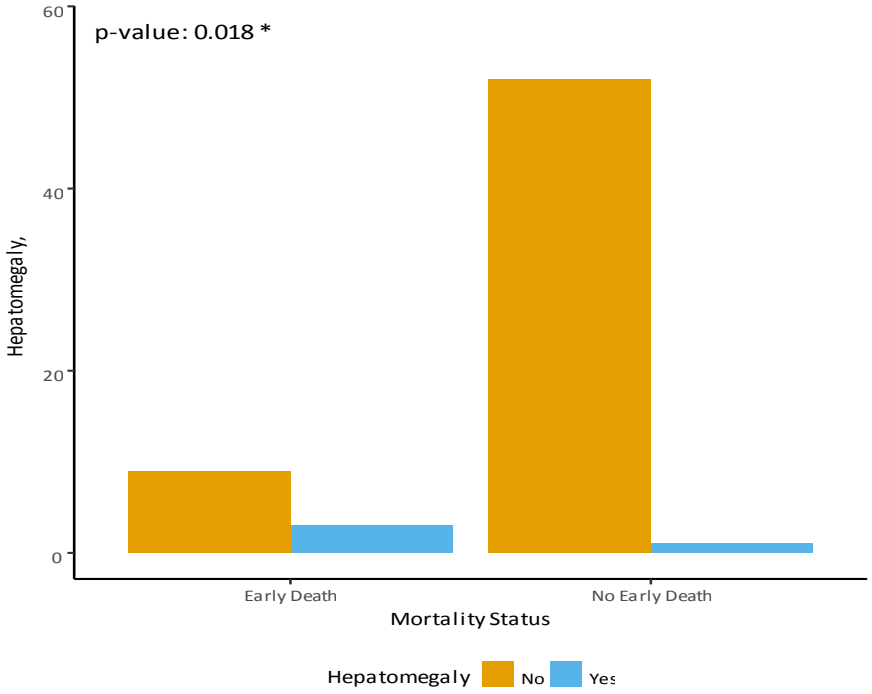

Figure 2 - Baseline comparison of subjects by short-term mortality status: Hepatomegaly

As for **long-term mortality**, **hepatomegaly was observed in 15.4% of the patients that died**, but unremarkable in the survivors; again statistical power was achieved (P-value=0.022).

8.2.7. THERAPEUTICS

A trend towards angiotensin-converting-enzyme (ACE) inhibitor use and improved long-term survival was perceived in the general population study and in the HFmrEF subgroup (HR: 0.277, 95% CI: 0.050-1.535, P-value= 0.142).

8.2.8. MODIFIABLE CARDIOVASCULAR RISK FACTORS- THE METABOLIC SYNDROME

Concerning cardiovascular (CV) risk factors, a trend towards dyslipidemia and risk of early readmission was identified in the subset of patients with HFrEF subgroup (HR: 3.952, 95% CI: 0.761-20.524, P-value= 0.102).

We detected a trend towards long-term mortality and dyslipidemia in the HFmrEF group HR: 5.346, 95% CI: 0.622-45.919, P-value=0.127).

A trend towards long-term mortality and diabetes, limited to the ischemic cardiomyopathy subgroup, was perceived (HR: 1.909, 95% CI: 0.738-4.940, P-value=0.183).

A trend towards obesity and improved long-term survival was observed (HR: 0.436, 95% CI: 0.150-1.266, P-value=0.127) and a trend towards better short-term survival and higher BMI was identified in the HFpEF group (HR: 0.784, 95% CI: 0.570-1.077, P-value=0.133).

We verified a trend towards the number of metabolic comorbidities and short-term readmission in the general population study (HR: 1.293, 95% CI: 0.908-1.842, P-value=0.154) and in the HFpEF group (HR: 1.456, 95% CI: 0.826-2.564, P-value=0.194).

We acknowledged a trend towards the number of metabolic comorbidities and short-term mortality in the HFrEF subset of patients (HR: 0.471, 95% CI: 0.165-1.346, P-value=0.160).

8.2.9. OTHER RISK FACTORS

8.2.9.1. Blood Pressure

The mean systolic blood pressure of the patients that survived the first 90 days post-discharge was 147 ± 30.0 mmHg versus 125 ±24.7 mmHg in the decedents.

Univariate Cox regression revealed that, in general population study, the **hazard of short-term mortality for patients with systolic blood pressure <100 mmHg was 5.3 times higher** than that for patients with systolic blood pressure ≥ 100 mmHg (HR=5.330, 95% CI: 1.407-20.193, P-value=0.014).

Figure 3 describes the Kaplan Meier short-term mortality curve for systolic blood pressure <100 mmHg.

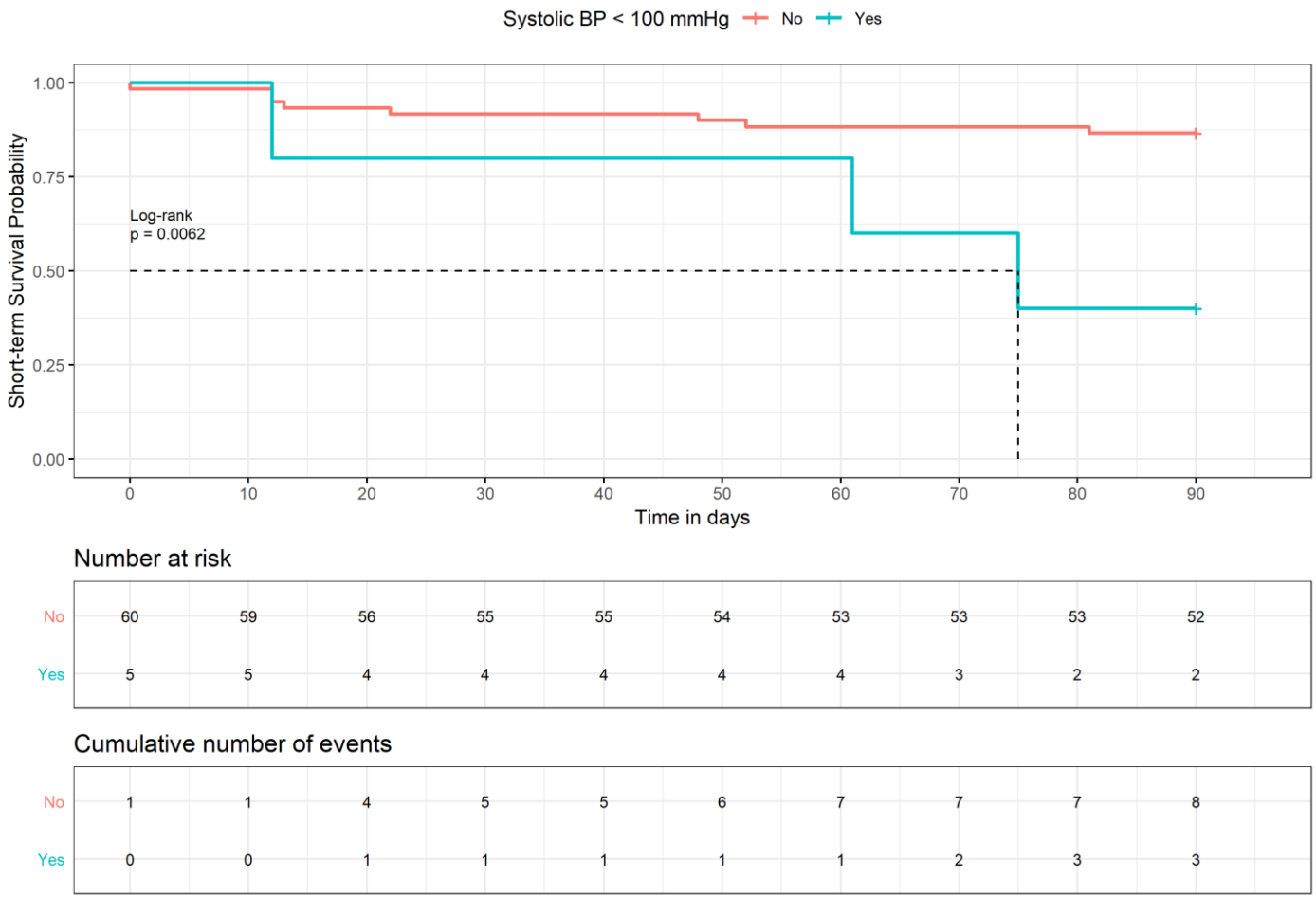

Figure 3 - Short-term mortality - Kaplan Meier: Systolic blood pressure <100 mmHg

As shown in Figure 4, the mean systolic blood pressure was significantly lower in the long-term mortality group than in the patients who survived (mean 149 ± 30.9 mmHg in the survivors versus 134 ± 27.2 mmHg in the deceased).

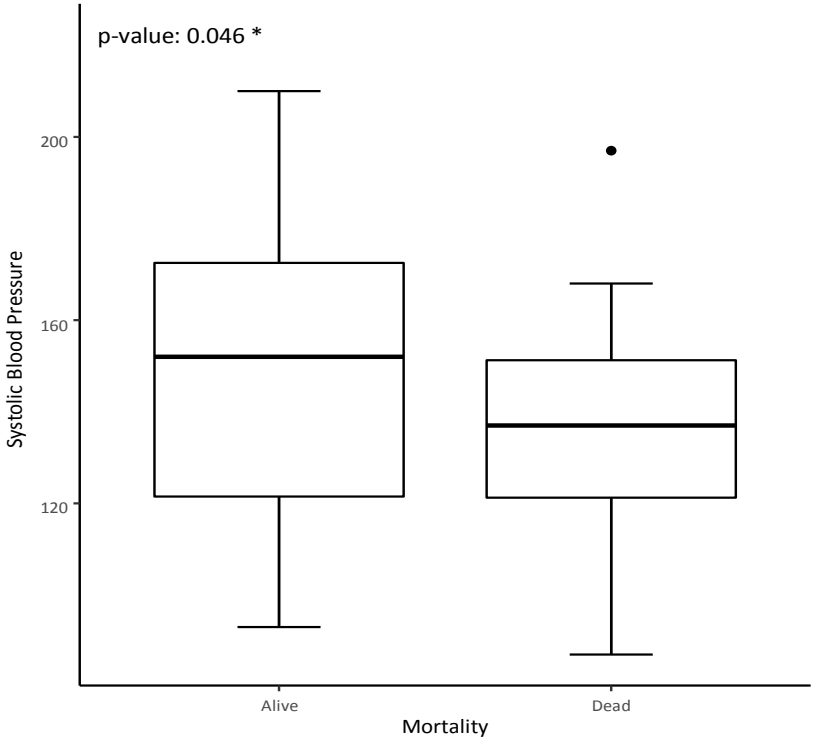

Figure 4 - Baseline comparison of subjects by long-term mortality status: Systolic blood pressure

Comparatively to short-term mortality, for the referred value of systolic blood pressure (i.e. <100 mmHg) **the risk declined to 3.6 times** (HR: 3.629, 95% CI: 1.239-10.631, P-value=0.019).

Subgroup discrimination evidenced that long-term mortality hazard rose up to 6.3 times in the HFrEF subgroup (HR: 6.303, 95% CI: 1.224-32.452, P-value=0.028).

Regarding diastolic blood pressure, Figure 5 depicts that the mean diastolic blood pressure was significantly lower (P-value=0.014) in the patients who died precociously compared to those who survived the early post-discharge period (mean 80 ± 19.9 mmHg in the survivors versus 69 ± 10.6 mmHg in the decedents).

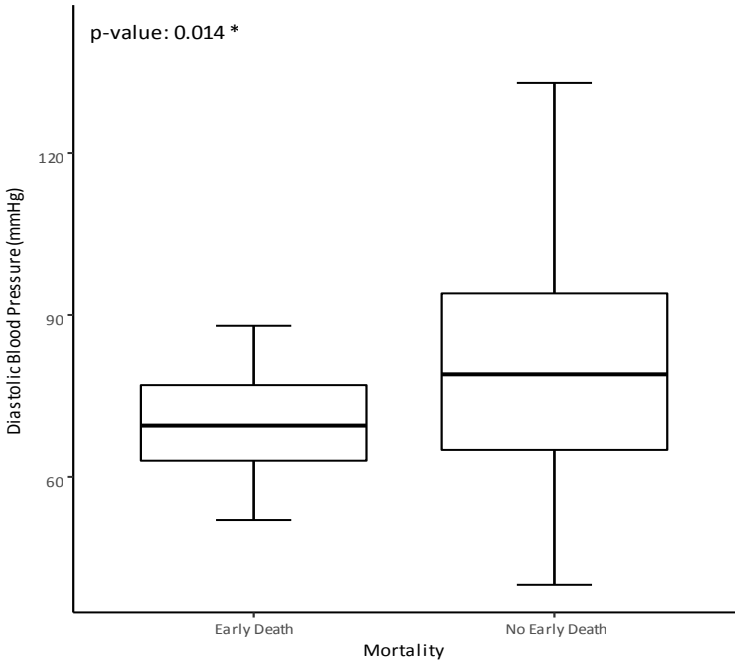

Figure 5 - Baseline comparison of subjects by short-term mortality status: Diastolic blood pressure

The univariate Cox proportional hazard model estimated an **increased risk of 11.1 times for short-term mortality in the HFrEF patients with diastolic blood pressure <60 mmHg** (HR: 11.116, 95% CI: 1.000-123.564, P-value=0.05).

During follow-up the hazard declined to 8.5 times in the mentioned subgroup (HR: 8.462, 95% CI: 1.662-43.096, P-value=0.010).

8.2.9.2. Renal Function

Chronic kidney disease was an important clinical prior regarding short-term mortality, being present in 45.3% of the survivors versus 83.3% of the decedents (P-value=0.024), as illustrated in Figure 6.

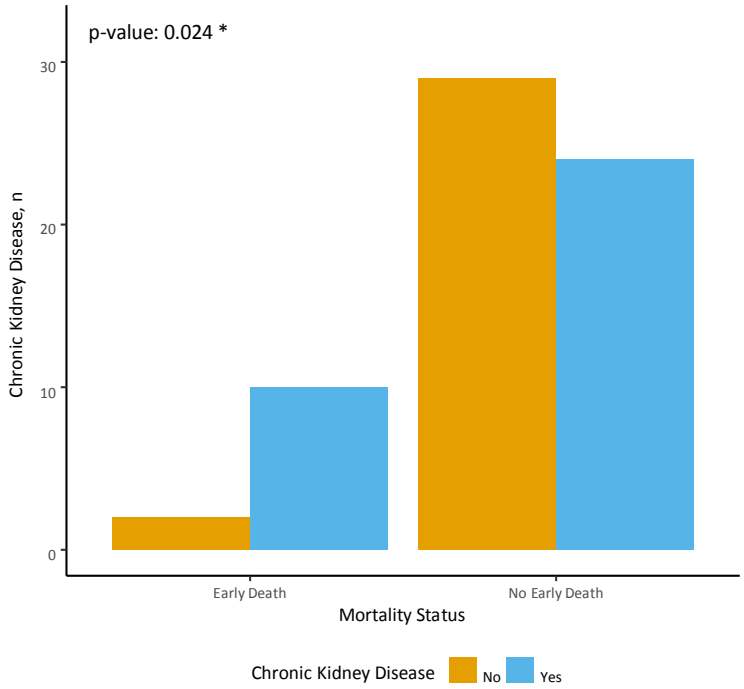

Figure 6 - Baseline comparison of subjects by short-term mortality status: Chronic kidney disease

Regarding **short-term readmission**, median **baseline urea** in the non-early readmitted group was 44 (33-62) mg/dL versus 70 (44-84) mg/dL in the early readmitted group; and **admission urea** was 51 mg/dL (36-76) versus 92 (48-128) mg/dL for the referred groups, respectively.

As for **short-term survival**, median **baseline urea** in the patients who survived the first 90 days post-discharge was 44 (34-67) mg/dL versus 73 (66-89) mg/dL in those who died in that period; median **admission urea** was 54 (35-80) mg/dL versus 104 (74-143) mg/dL for the same groups, respectively.

Minding **long-term survival**, median **baseline urea** was 44 (35-64) mg/dL in the survivors versus 70 (41-84) mg/dL in those who died during follow-up; whereas median **admission urea** was 49 (34-74) mg/dL in the survivors versus 83 (50-124) mg/dL in those who died along follow-up.

Median **baseline creatinine** in the non-early readmitted group was 1.0 mg/dL (0.8-1.2) versus 1.3 mg/dL (1.0-1.5) in the **early readmitted** group; while **admission creatinine** was 1.3 mg/dL (1.0-1.6) versus 1.6 mg/dL (1.1-2.3) for the mentioned groups, respectively.

Considering **early mortality**, median **baseline creatinine** in the patients who survived the first 90 days post-discharge was 1.0 (0.8-1.3) mg/dL versus 1.4 (1.2-1.5) mg/dL in those who died in that period; median **admission creatinine** was 1.2 (0.9-1.7) mg/dL versus 2.4 (1.6-2.7) mg/dL for the given subset of patients (Figure 7).

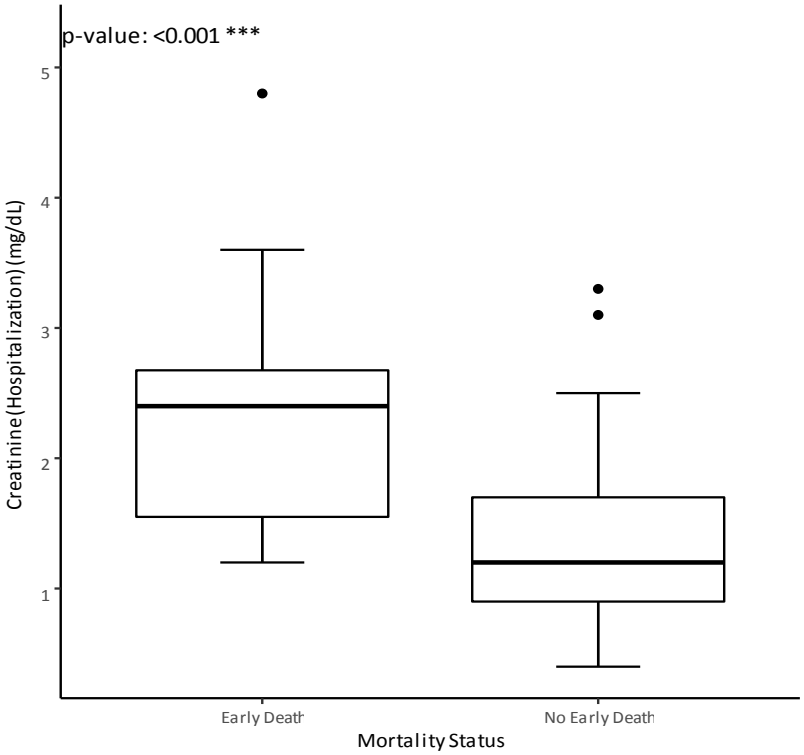

Figure 7 - Baseline comparison of subjects by short-term mortality status: Admission creatinine

In what matters to **long-term mortality**, median **baseline creatinine** in the patients who survived was 1.0 (0.8-1.3) mg/dL versus 1.2 (0.9-1.5) mg/dL in the group that died; while median **admission creatinine** was 1.2 (1.0-1.5) mg/dL in the survivors versus 1.7 (1.3-2.6) mg/dL in those who died through follow-up.

Referring to **early readmission**, median **baseline GFR** in the non-early readmitted group was 65.8 mL/min (48.1-83.3) versus 49.3 mL/min (41.1-74.7) mL/min in the early readmitted group; a median **admission GFR** of 56.5 mL/min (35.6-69.1) versus 36.5 mL/min (23.4-54.5) was found in the considered groups.

Addressing **short-term mortality**, median **baseline GFR** in the early death group was 67.8 (47.3-83.5) mL/min versus 44.3 (35.6-50.5) in the group that died; while a median **admission GFR** of 56.5 (36.0-71.5) mL/min versus 23.4 (18.9-34.4) mL/min was observed in the two groups, respectively.

Descriptive analysis showcased a median **baseline GFR** of 68.6 (47.3-84.4) mL/min in the survivors versus 50.9 (41.8-74.5) mL/min in **those who died throughout follow-up**.

The same statistical method demonstrated a median **admission GFR** of 56.5 (35.0-72.4) mL/min in the survivors versus 39.0 (20.0-57.6) mL/min in **those who died along follow-up**.

The hazard for short-term rehospitalization increased 9.8% per 5 mg/dL increment of baseline urea (HR: 1.098, 95% CI: 1.022-1.179, P-value=0.01).

The risk for short-term rehospitalization augmented 4.8% per 5 mg/dL increment of admission urea (HR: 1.048, 95% CI: 1.013-1.084, P-value=0.006).

An association between elevated baseline creatinine and early readmission was noticed (HR: 1.111, 95% CI: 1.004-1.229, P-value=0.041), the risk augmented 11.1% per 0.1 mg/dL increment of creatinine.

In relation to admission creatinine, the risk for early readmission augmented 4.7% per 0.1 mg/dL increment of creatinine (HR: 1.047, 95% CI: 1.005-1.092, P-value=0.027).

Early readmission hazard increased 3.5 times with admission GFR <30 mL/min (HR: 3.535, 95% CI: 1.467-8.518, P-value=0.005).

With reference to short-term mortality the results were also interesting as both baseline and admission urea were significant risk predictors (HR: 1.145, 95% CI: 1.032-1.270, P-value=0.010, determining a 14.5% additional risk per increments of 5 mg/dL and HR: 1.076, 95% CI: 1.021-1.135, P-value=0.006, implicating a 7.6% increased risk per increments of 5 mg/dL, respectively).

As for admission creatinine for each 0.1 mg/dL increment the risk for short-term mortality augmented 12.7% (HR: 1.127, 95% CI: 1.055-1.204, P-value<0.001), for the same amount of increase for baseline creatinine the risk augmented 15.7% (HR: 1.157, 95% CI: 1.009-1.328, P value=0.037).

Hazard analysis by subgroup of HF showed that for short-term mortality, focusing on HFrEF patients, the risk augmented 15.1% per 0.1 mg/dL increment of hospitalization creatinine (HR: 1.151, 95% CI: 1.010-1.311, P- value=0.034).

It is important to stress that admission GFR <30 ml/min increased the likelihood of early death 9.8 times in the entire population study (HR: 9.791, 95% CI: 2.855-33.580, P-value<0.001) and rose the risk up to 14.8 times in the HFrEF subgroup (HR: 14.783, 95% CI: 1.267-172.493, P-value=0.032).

On the subject of long-term mortality, admission urea elevated the hazard 5.6% per increments of 5 mg/dL (HR: 1.056, 95% CI: 1.019-1.094, P-value=0.003) in the total population study.

In the HFrEF subgroup long-term mortality risk increased 10.5 % per increments of 5 mg/dL of admission urea (HR: 1.105, 95% CI: 1.037-1.177, P value=0.002) and 13.2% per increments of 5 mg/dL of baseline urea (HR: 1.132, 95% CI: 1.004-1.276, P value=0.042).

With regard to long-term mortality admission creatinine worsened the outcome 10.4% per increments of 0.1 mg/dL (HR: 1.104, 95% CI: 1.054-1.156, P- value<0.001) in the general population study, whereas in the subgroup of HFpEF the risk for this end-point was inferior, as per increments of 0.1 mg/dL of admission creatinine the risk raised only 8% (HR: 1.080, 95% CI: 1.007-1.159, P-value=0.032).

Interestingly, in the HFrEF subgroup long-term mortality risk was greatest, since it increased 14.8% per increments of 0.1 mg/dL of admission creatinine (HR: 1.148, 95% CI: 1.051-1.253, P-value=0.002).

Higher admission GFR decreased long-term mortality hazard around 20% per increments of 10 mL/min (HR: 0.788, 95% CI: 0.649-0.957, P-value=0.016) in the global population study. As for the HFrEF subgroup long-term mortality risk diminished 41% per increments of 10 mL/min of admission GFR (HR: 0.590, 95% CI: 0.365-0.953, P-value=0.031).

Admission GFR <30 ml/min increased the hazard 3.9 times (HR: 3.906, 95% CI: 1.7208.871, P-value=0.001), while for admission GFR <15 ml/min the risk ascended to 6.1 times (HR: 6.087, 95% CI: 1.403-26.402, P-value=0.016) in the overall population study.

Minding the subgroup of HFpEF, long-term mortality correlated with admission GFR <30 ml/min (HR: 3.640, 95% CI: 1.073-12.351, P-value=0.038) and in the HFrEF subgroup for admission GFR <30 mL/min this outcome risk augmented 13 times (HR: 13.387, 95% CI: 2.356-76.075, P value=0.003).

Cardiorenal syndrome was present in 63.6% of the early readmitted patients, compared to 48.8% in the group not rehospitalized, notwithstanding statistical significance was not observed.

Descriptive analysis showed a prevalence of **cardiorenal syndrome twice as superior in the short-term mortality group** compared to those who survived (91.7% versus 45.3%, respectively, P-value=0.004).

The Kaplan Meier short-term mortality curve for cardiorenal syndrome is illustrated ahead (Figure 8).

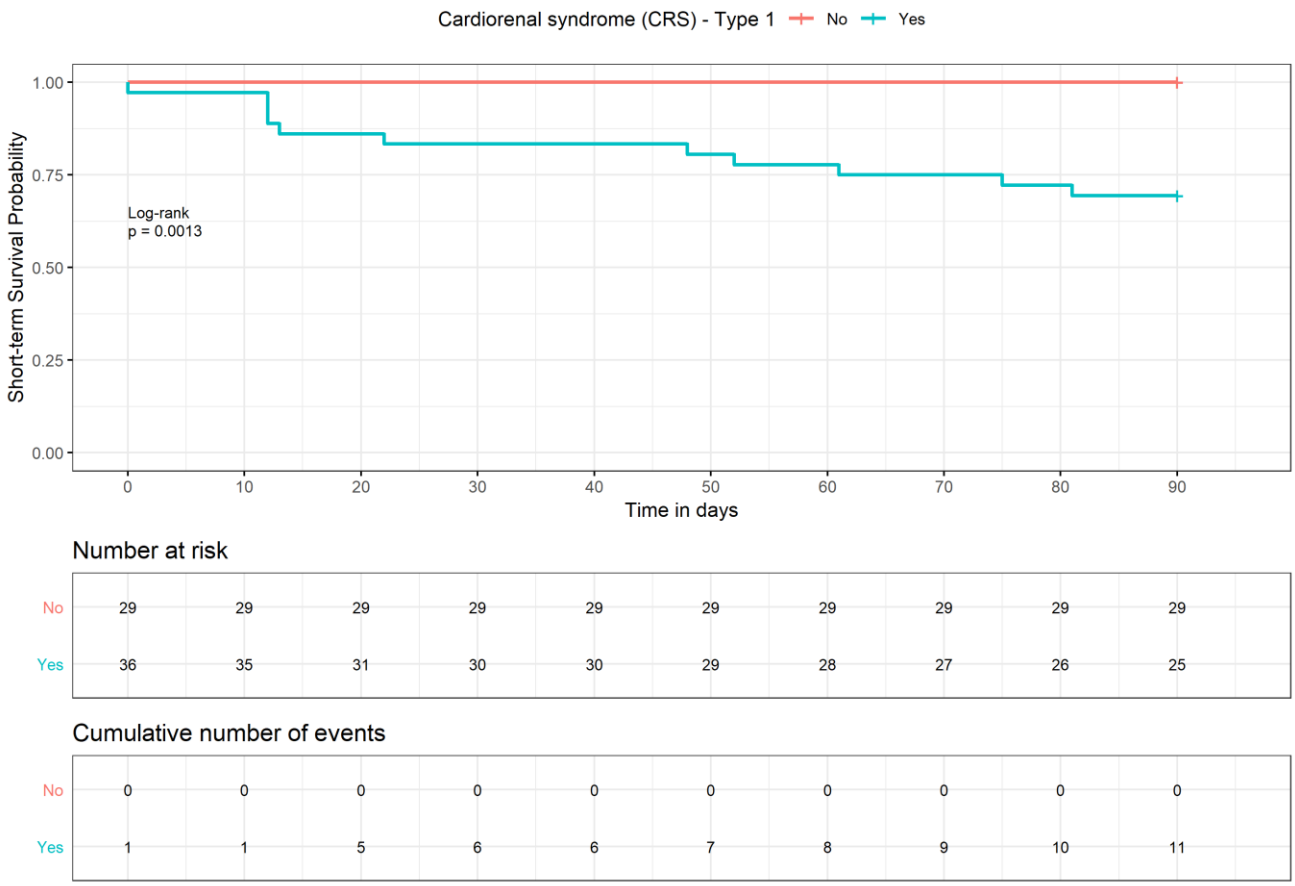

Figure 8 - Short-term mortality - Kaplan Meier: Cardiorenal syndrome

Descriptive analysis comparison revealed a 73.1% prevalence of cardiorenal syndrome in the long-term mortality group versus 41% in the survivors (P-value=0.011).

The presence of **cardiorenal syndrome increased long-term mortality risk around 2.6 times** in the global population study (HR: 2.582, CI: 1.120-5.950, P-value=0.026), achieving a 73.1% prevalence in the decedents and 41% in the survivors.

As anticipated, long-term mortality hazard was superior in the HFrEF subgroup (HR: 8.567, 95% CI: 1.034-70.981, P-value=0.046).

8.2.9.3. Atrial Fibrillation

In our study no connection was acknowledged between atrial fibrillation (AF) and the proposed outcomes.

8.2.9.4. Bundle Branch Block

Left bundle branch block (LBBB) determined a short-term mortality risk 3.4 times superior (HR: 3.444, 95% CI: 1.051-11.293, P-value=0.041). It was present in 41.7% of the patients that died early, while it was present in only 17% of those that survived.

The Kaplan Meier short-term mortality curve for LBBB is represented in Figure 9.

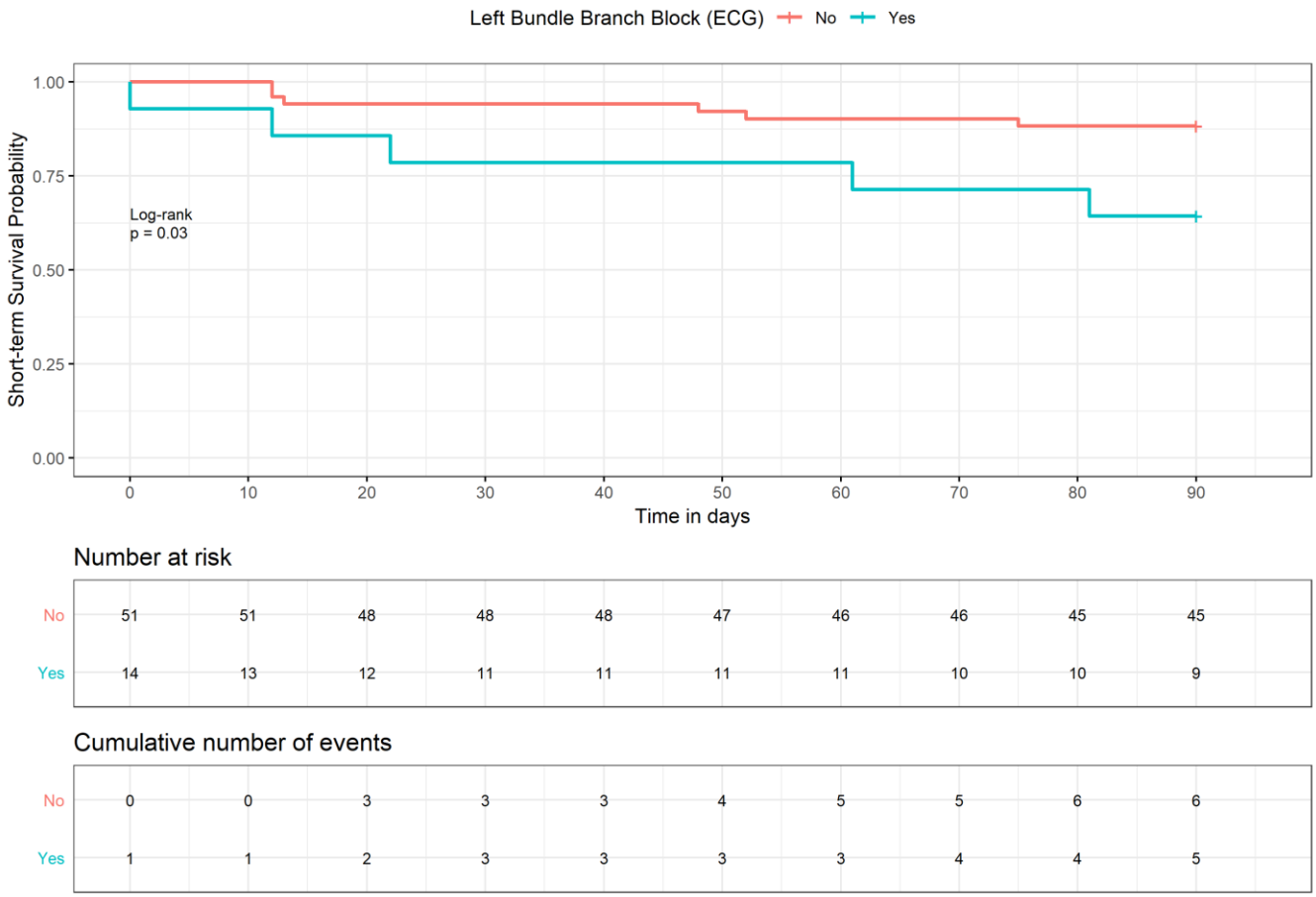

Figure 9 - Short-term mortality - Kaplan Meier: LBBB

Apropos of **long-term survival**, **HFrEF patients with LBBB showed a HR of 4.1** (HR: 4.140, 95% CI: 1.021-16.790, P-value=0.047).

Descriptive analysis identified that only 4.7% of the non-early readmitted patients presented **right bundle branch block (RBBB)** versus **13.6% in the early readmitted** patients (P-value=0.049).

8.2.9.5. Hyponatremia

Univariate Cox regression analysis found that, in HFmrEF patients with sodium <137 meq/L, the risk of early readmission was around 10 times greater. This association marginally missed statistical significance (P-value=0.053).

8.2.9.6. Free Thyroxine

Survival analysis showed a trend towards higher free thyroxine (FT4) levels and decreased early readmission risk in the HFmrEF subgroup (HR: 0.003, 95% CI: 0.000 -13.314, P-value=0.176).

The mentioned statistical method identified a trend towards greater FT4 serum values and better short-term mortality rates in the HFrEF subgroup (HR: 0.008, 95% CI: 0.000 -2.939, P-value=0.108).

Regarding **long-term mortality**, a trend towards **higher FT4** serum values and lower risk, close to reaching statistical impact (HR: 0.210, 95% CI: 0.042-1.050, P-value=0.057), was acknowledged in the general population study, while statistical significance was met **in the HFrEF subgroup** (HR: 0.003, 95% CI: 0.000-0.411, P-value=0.020).

8.2.9.7. Anemia and Iron Deficiency

The mean hemoglobin value for the non-early readmitted patients was 12.1 g/dL ± 1.8 versus 10.9 ± 1.8 g/dL in the early readmitted group (Figure 10). Such difference between groups was statistically significant (P-value=0.012).

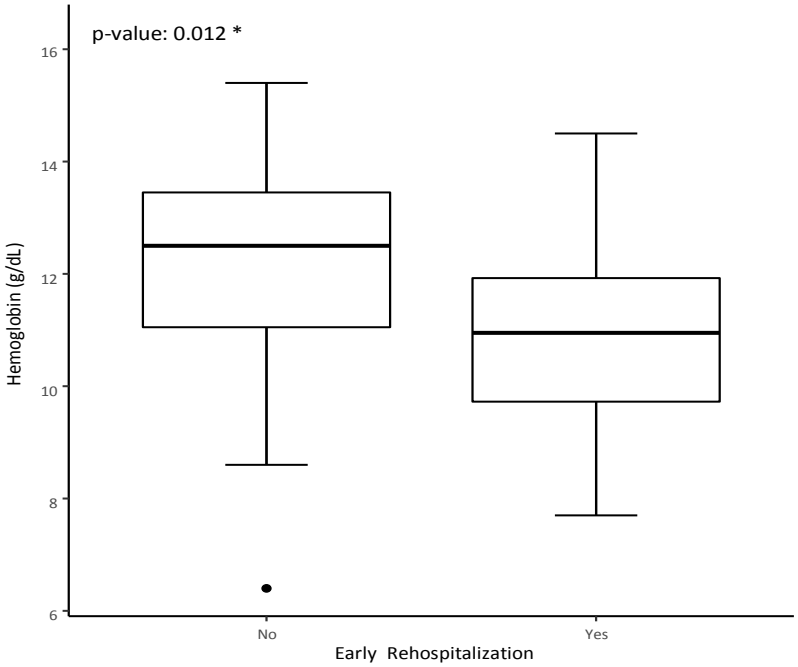

Figure 10 - Baseline comparison of subjects by early rehospitalization status: Hemoglobin

After survival analysis, **anemia** (defined as hemoglobin <12 g/dL) **tripled the risk for short-term readmission** (HR: 3.200, 95% CI: 1.249-8.196, P-value=0.015) **and with the delineation of gender thresholds**, (i.e. females <12 g/dL and males <13 g/dL) **a little increase of the risk was observed** (HR: 3.809, 95% CI: 1.287-11.275, P-value=0.016).

Subgroup analysis demonstrated a greater short-term readmission risk for the HFrEF group for values of hemoglobin <12 g/dL (HR: 5.425, 95% CI: 1.006-29.251, P-value=0.049). Once again, gender related thresholds revealed an increase of the risk (HR: 9.183, 95% CI: 1.083-77.878, P-value=0.042).

Respecting **long-term mortality**, **in the HFrEF subgroup**, **anemia** (defined as hemoglobin <12 g/dL) **increased the risk up to 6.9 times** (HR: 6.868, 95% CI: 1.337-35.278, P-value=0.021). Sex thresholds, as described above, further increased the risk (HR: 11.144, 95% CI: 1.349-92.069, P-value=0.025).

Descriptive analysis revealed a median serum ferritin of 185.7 (64.0-374.2) ng/mL in the subset of patients that survived the first 90 days post-discharge versus 64.7 (38.2 - 90.8) ng/mL in the group that died in that length of time.

Besides, applying hazard evaluation, **serum ferritin <100 ng/mL determined a 7.2 increased risk of short-term mortality** (HR: 7.220, 95% CI: 1.497-34.809, P-value=0.014).

Figure 11 represents the Kaplan Meier short-term mortality curve for serum ferritin <100 ng/mL.

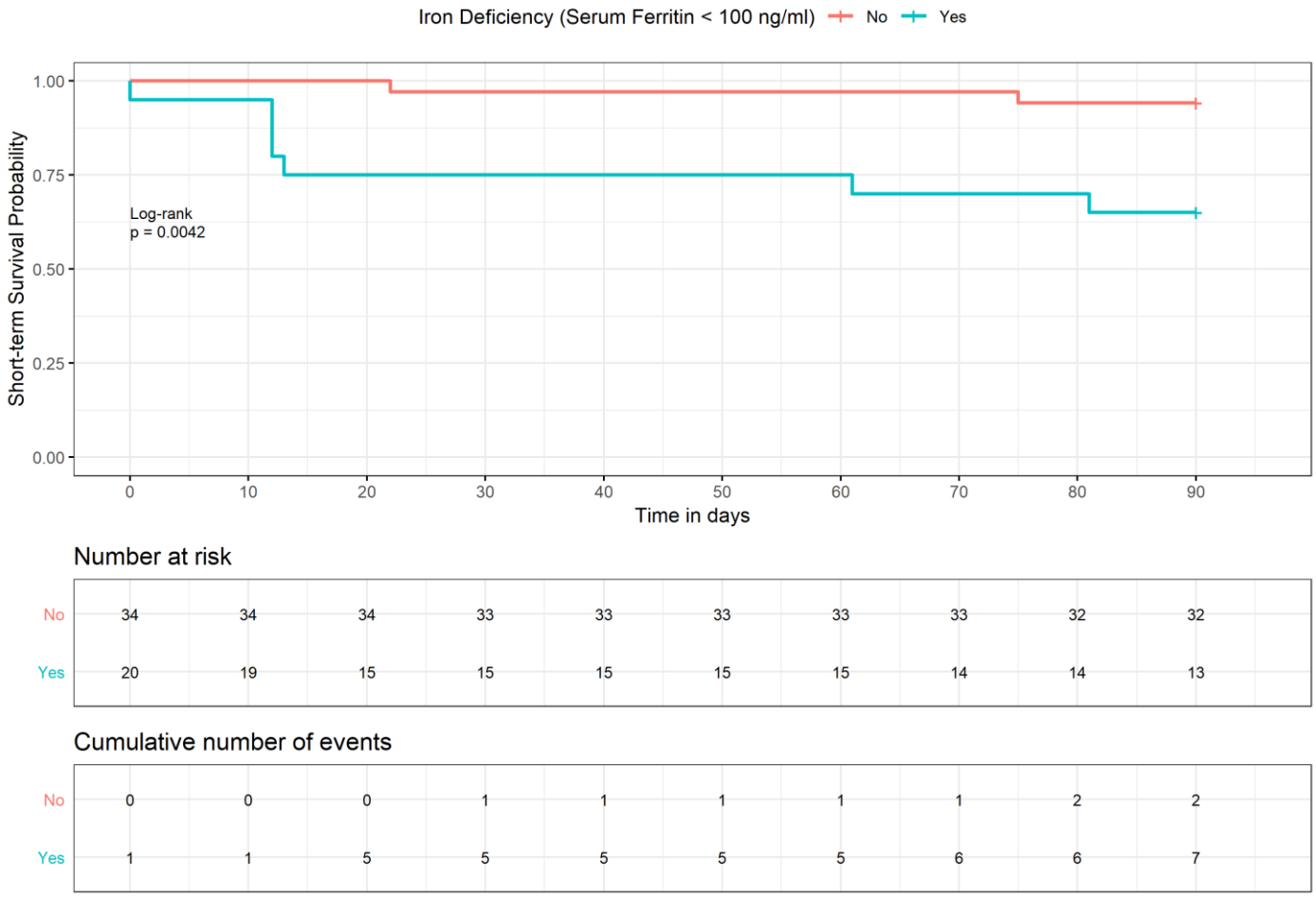

Figure 11 - Short-term mortality - Kaplan Meier: Serum ferritin <100 ng/mL

In the HFrEF subgroup elevated serum iron was a protective factor as per each increase of 10 ug/dL short-term mortality risk decreased 65.8% (HR: 0.342, 95% CI: 0.119-0.982, P-value=0.046).

In HFpEF patients a trend towards increased total iron binding capacity and early rehospitalization was detected (HR: 0.913, 95% CI: 0.822-1.014, P-value=0.090).

8.2.9.8. Red Cell Distribution Width

Figure 12 demonstrates that the median red cell distribution width (RDW) in the non-early readmitted subgroup was 14.8 (13.8-15.4) % compared to 16.1 (14.5-17.6) % in the early readmitted subgroup (P-value=0.009).

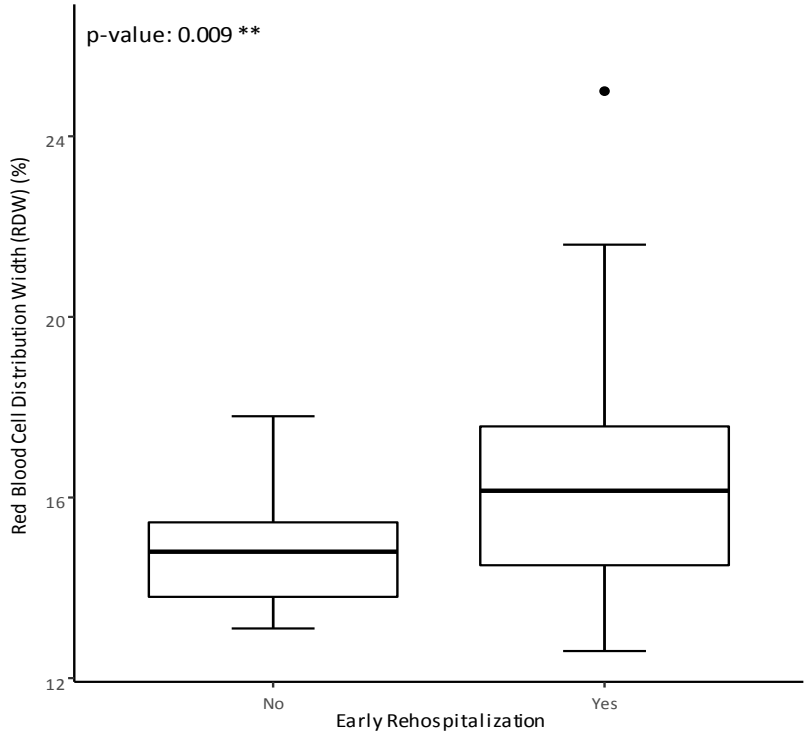

Figure 12 - Baseline comparison of subjects by early rehospitalization status: RDW

Further hazard analysis demonstrated that **RDW was a predictor of early readmission** (HR: 1.350, 95% CI: 1.155-1.577, P- value<0.001).

As expected, in the subset of patients with HFpEF the early readmission hazard was inferior to that of the general population (HR: 1.301, 95% CI: 1.070-1.581, P value=0.008).

Moreover, **RDW was, as well, a predictor of early and long-term mortality**.

Median RDW in the patients that survived the first 90 days post-discharge was 14.9 (13.8-15.7) % versus 17.0 (14.9-17.7) % in the group that died precociously and median RDW in the patients that survived throughout follow-up was 14.8 (13.8-15.6) % versus 15.5 (14.8-17.2) % in the group that died.

The risk decreased during follow-up (HR: 1.826, 95% CI: 1.288-2.588, P-value<0.001 for early mortality versus HR: 1.294, 95% CI: 1.098-1.525, P value=0.002 for long-term mortality).

In the particular case of the HFrEF subgroup, once more, long-term mortality risk was superior to overall populations' (HR: 1.480, 95% CI: 1.098-1.995, P value=0.01).

8.2.9.9. Erythropoietin

A trend towards short-term readmission and elevated erythropoietin values was recognized in both total population study (HR: 1.064, 95% CI: 0.994-1.140, P-value=0.074) and in HFrEF patients (HR: 1.084, 95% CI: 0.992-1.185, P-value= 0.074).

According to descriptive analysis, the median EPO value in the group of patients that survived the first 90 days post-discharge was 14.12 (9.56-20.18) mU/mL compared to 33.04 (16.30-58.26) mU/mL in the group that died early.

Moreover, **per increments of 10 mU/mL the risk for short-term mortality increased 37.7%** (HR: 1.377, 95% CI: 1.043-1.816, P-value=0.024).

The median erythropoietin value in the group of patients that survived through follow-up was 11.97 (7.99-16.44) mU/mL versus 19.46 (15.15-50.98) mU/mL in the group that died (P-value=0.002). Figure 13 represents these results.

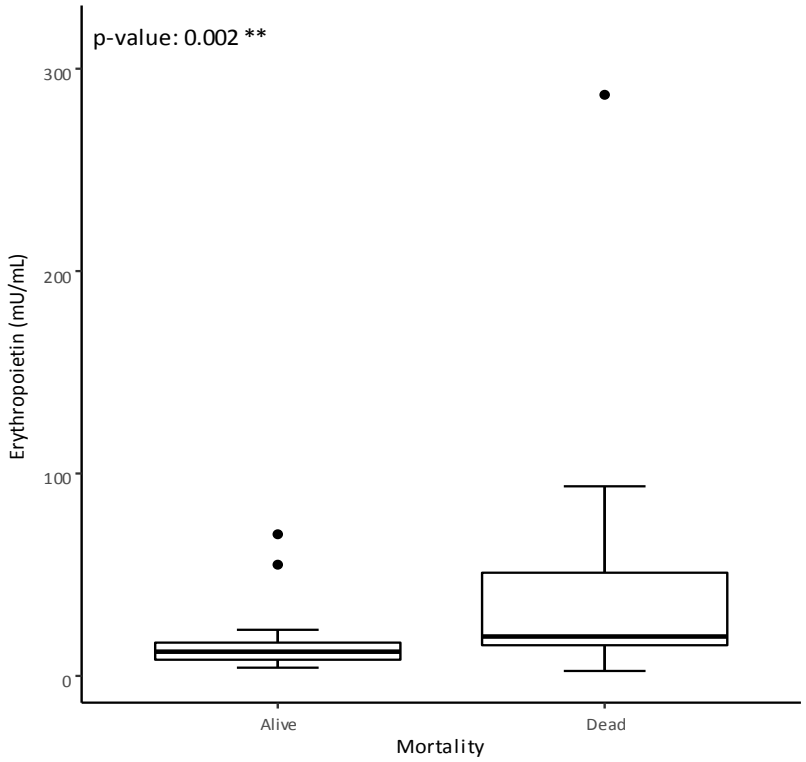

Figure 13 - Baseline comparison of subjects by long-term mortality status: EPO

Mortality risk reduced along follow-up given that **for long-term mortality the risk increased 28.5% per increments of 10 mU/mL** (HR: 1.285, 95% CI: 1.105-1.494, P-value=0.001).

Further analysis per subgroup of HF regarding long-term mortality, showed that in the HFrEF subgroup, the risk augmented 81.4% per increments of 10 mU/mL (HR: 1.814, 95% CI: 1.141-2.884, P-value=0.012) and a trend towards increased risk was noted in the HFpEF subgroup (HR: 1.295, 95% CI: 0.933-1.796, P-value=0.122).

8.3. BIOMARKERS

8.3.1. BRAIN NATRIURETIC PEPTIDES

The plasma **concentration of NT-proBNP was lower in the obese** [median 7588 (2544-15815) ng/L for non-obese versus 1475 (918.5-5643) ng/L for the obese, P-value=0.006)].

Spearman's correlation showed an **inversely proportional relation between NT-proBNP and LVEF** (Coefficient: -0.365, P-value=0.004).

The same statistical method evidenced an **inverse correlation between NT-proBNP and baseline and admission GFR** (Coefficient: -0.418, P-value<0.001 for baseline GFR and Coefficient: -0.438, P-value<0.001 for admission GFR).

The median admission NT-proBNP in the patients that survived the first 90 days post-discharge was 4993 (1730-11260) ng/L versus 9302 (4104-24502) ng/L in the short-term mortality group.

The **hazard of short-term mortality increased 0.5% per increments of 100 ng/L of admission NT-proBNP** (HR: 1.005, 95% CI: 1.002-1.009, P-value=0.002) and with a **cut-off value of 21336 ng/L the mortality risk was 10.5 times greater** (HR: 10.524, 95% CI: 3.013-36.757, P-value<0.001).

Descriptive analysis revealed that the long-term mortality group had significant (P-value=0.022) higher values of admission NT-proBNP compared to those who survived [median 9302 (3917-20452) ng/L in the group that died during follow-up versus 4340 (1278-8031) ng/L in the group that survived]. Such findings are expressed in Figure 14.

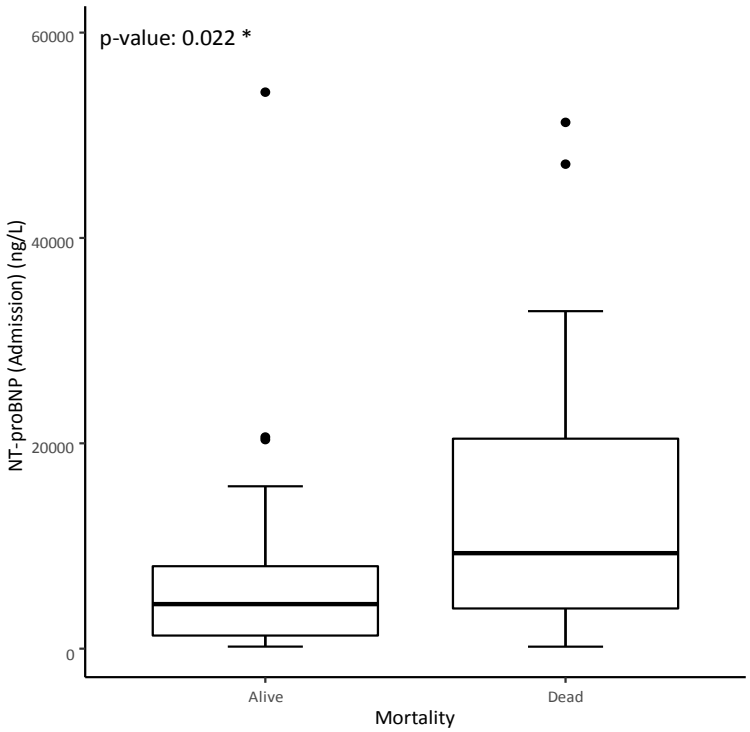

Figure 14 - Baseline comparison of subjects by long-term mortality status: Admission NT-proBNP

Survival analysis exposed a **risk for long-term mortality close to 5 times with admission determinations ≥21336 ng/L** (HR: 4.791, 95% CI: 1.885-12.178, P-value<0.001).

Additional analysis documented that **the hazard for long-term mortality increased 0.3% per increments of 100 ng/L of admission NT-proBNP** (HR: 1.003, 95% CI: 1.001-1.006, P-value=0.013).

Figure 15 portrays that there was a significant difference (P-value=0.045) in the median **discharge values of NT-proBNP** between the **long-term mortality** group and those that survived [median 4773 (1267-8424) ng/L in the group that died compared to 1524 (311-4432) ng/L for the survivors].

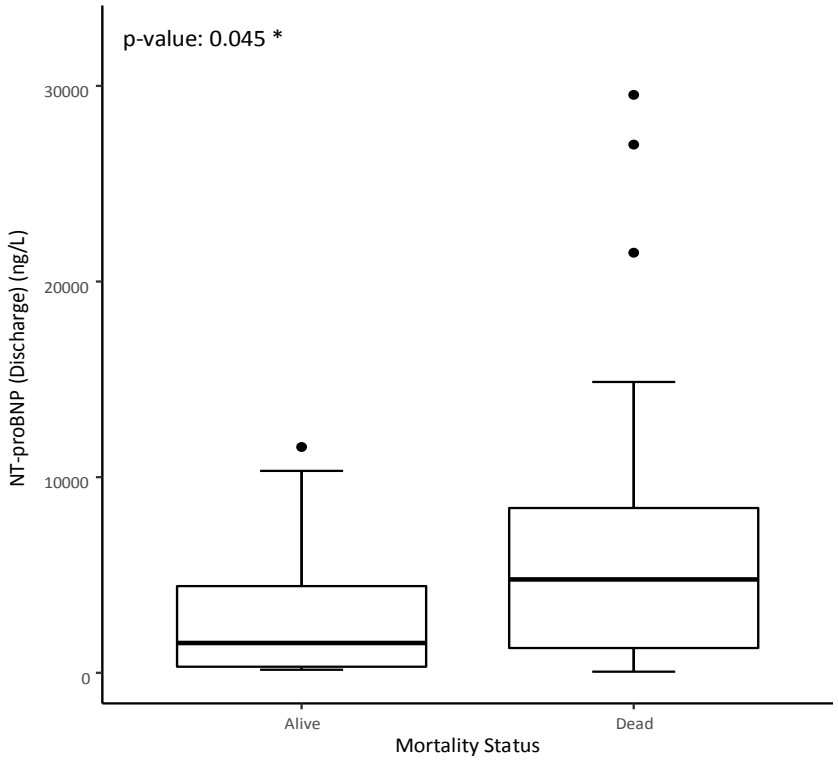

Figure 15 - Baseline comparison of subjects by long-term mortality status: Discharge NT-proBNP

Univariate Cox regression showed that **the risk increased 0.6% per increments of 100 ng/L of discharge NT-proBNP** (HR: 1.006, 95% CI: 1.001-1.011, P-value=0.028).

8.3.2. TROPONINS

Descriptive analysis estimated that the difference between the median hsTnT of the long-term mortality group and those that survived [median 108 (54-209) ng/L for the decedents compared to 39 (27-58) ng/L for the survivors] was statistically significant (P-value= 0.023).

Univariate Cox regression showcased that the **long-term mortality probability increased 7.7% per increments of 10 ng/L of hsTnT** (HR: 1.077, 95% CI: 1.007-1.151, P value=0.030).

We explored **the combination** of hsTnT and admission NT-proBNP and realized that for values **of hsTnT ≥52 ng/L and NT-proBNP ≥21336 ng/L the risk of early readmission increased 8.6 times** (HR: 8.607, 95% CI: 1.413-52.427, P-value=0.020).

As **for long-term mortality**, values of **hsTnT ≥52 ng/L aggravated the hazard close to 5 times** (HR: 4.942, 95% CI: 1.044-23.388, P value=0.044), **which heightened to almost 6 times if NT-proBNP at admission ≥21336 ng/L was considered** (HR: 5.827, 95% CI: 1.168-29.075, P value=0.032).

Figure 16 displays the Kaplan Meier long-term mortality curve for values of hsTnT ≥52 ng/L.

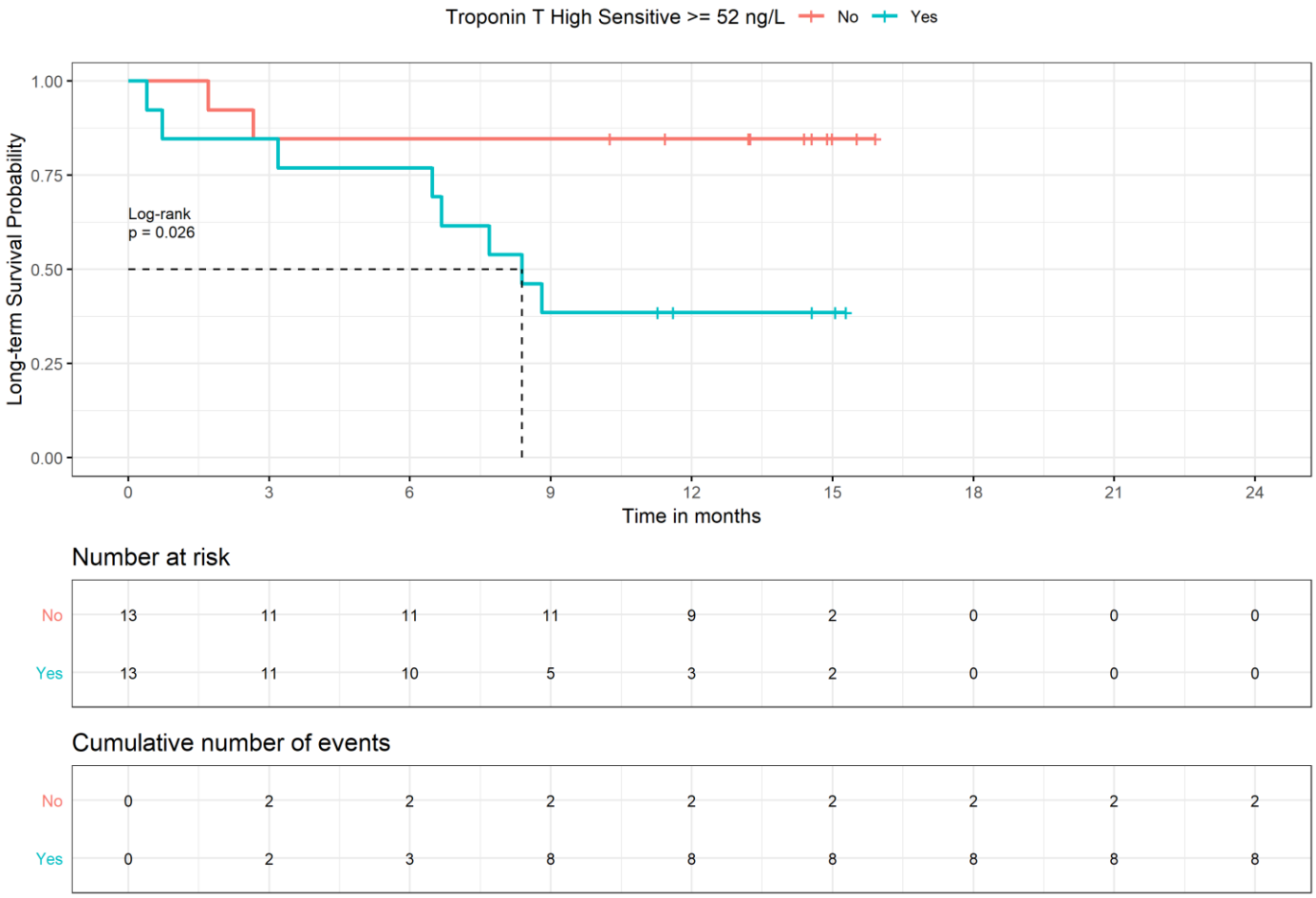

Figure 16 - Long-term mortality - Kaplan Meier: hsTnT ≥52 ng/L

8.3.3. GALECTIN-3

The Spearman's correlation coefficient was used to determine the relationship between Gal-3 and GFR, recognizing an **inversely proportional relation between Gal-3 levels and baseline GFR** (Coefficient: -0.537, P-value<0.001) **and admission GFR** (Coefficient: -0.549, P-value<0.001).

In contrast, Spearman's correlation revealed that **Gal-3 and NT-proBNP values were proportional** (Coefficient: 0.383, P-value=0.009).

A trend towards elevated Gal-3 determinations and ischemic heart disease was observed (median Gal-3 value for ischemic heart disease 11.4 (8.3 - 12.6) ng/mL versus 9.2 (6.6 - 11.0) ng/mL in the patients without ischemic heart disease (P-value=0.138).

Further analysis showed an **association between increased Gal-3** values **and short-term rehospitalization**.

The median Gal-3 value for non-early readmitted patients was 9.44 (7.30-10.96) ng/mL compared to 12.02 (11.41-12.62) ng/mL in the early readmitted patients, as shown in Figure 17.

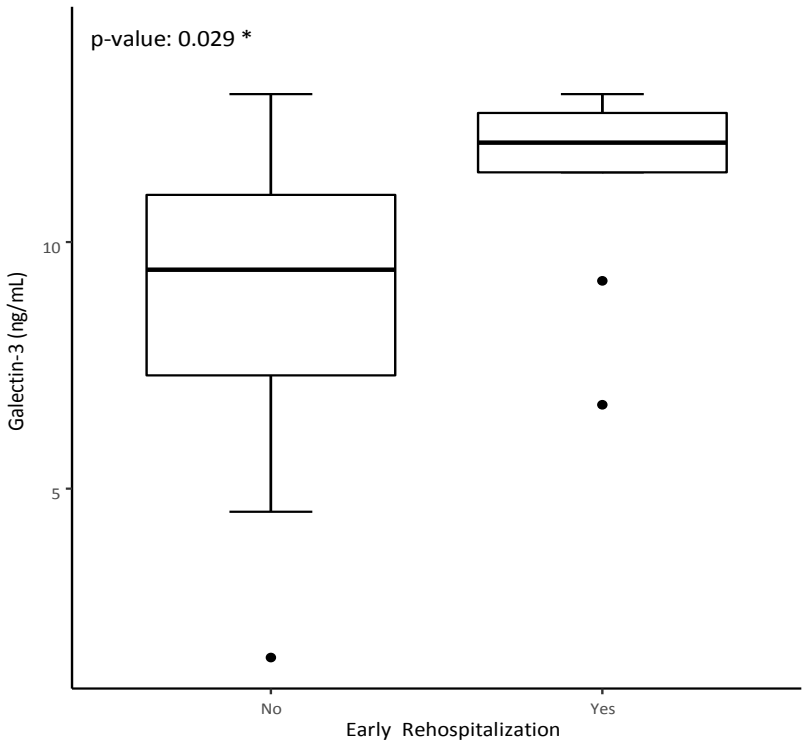

Figure 17 - Baseline comparison of subjects by early rehospitalization status: Gal-3

The analysis of the hazard ratios indicated an increased risk of 5.5 times for Gal-3 ≥9.99 ng/mL (HR: 5.449, 95% CI: 1.124-26.411, P-value=0.035), for Gal-3 ≥ 10.97 ng/mL the risk augmented 9.9 times (HR: 9.886, 95% CI: 2.027-48.214, P-value= 0.005) and for Gal-3 ≥11.41 ng/mL the risk augmented 11.8 times (HR: 11.762, 95% CI: 2.402-57.598, P-value=0.002).

If we added values of admission NT-proBNP ≥21336 ng/L to those of Gal-3 ≥10.97 ng/mL **the risk further increased up to 12 times** (HR: 11.985, 95% CI: 1.962-73.218, P value=0.007). For the HFrEF group the later determinations of NT-proBNP and Gal-3 represented a slightly superior risk of short-term rehospitalization (HR: 13.198, 95% CI: 1.165-149.465, P value= 0.037).

Descriptive analysis regarding **short-term survival** established a median Gal-3 of 9.31 (7.01-11.01) ng/mL in the group of patients that did not die early versus 12.59 (11.25-13.00) ng/mL in the short-term mortality group.

Complementary survival analysis identified a **13.7 times increased risk for values of Gal-3 ≥10.97 ng/mL** (HR: 13.731, 95% CI: 1.650-114.276, P value=0.015).

Figure 18 demonstrates the Kaplan Meier short-term mortality curve for values of Gal-3 ≥10.97 ng/mL.

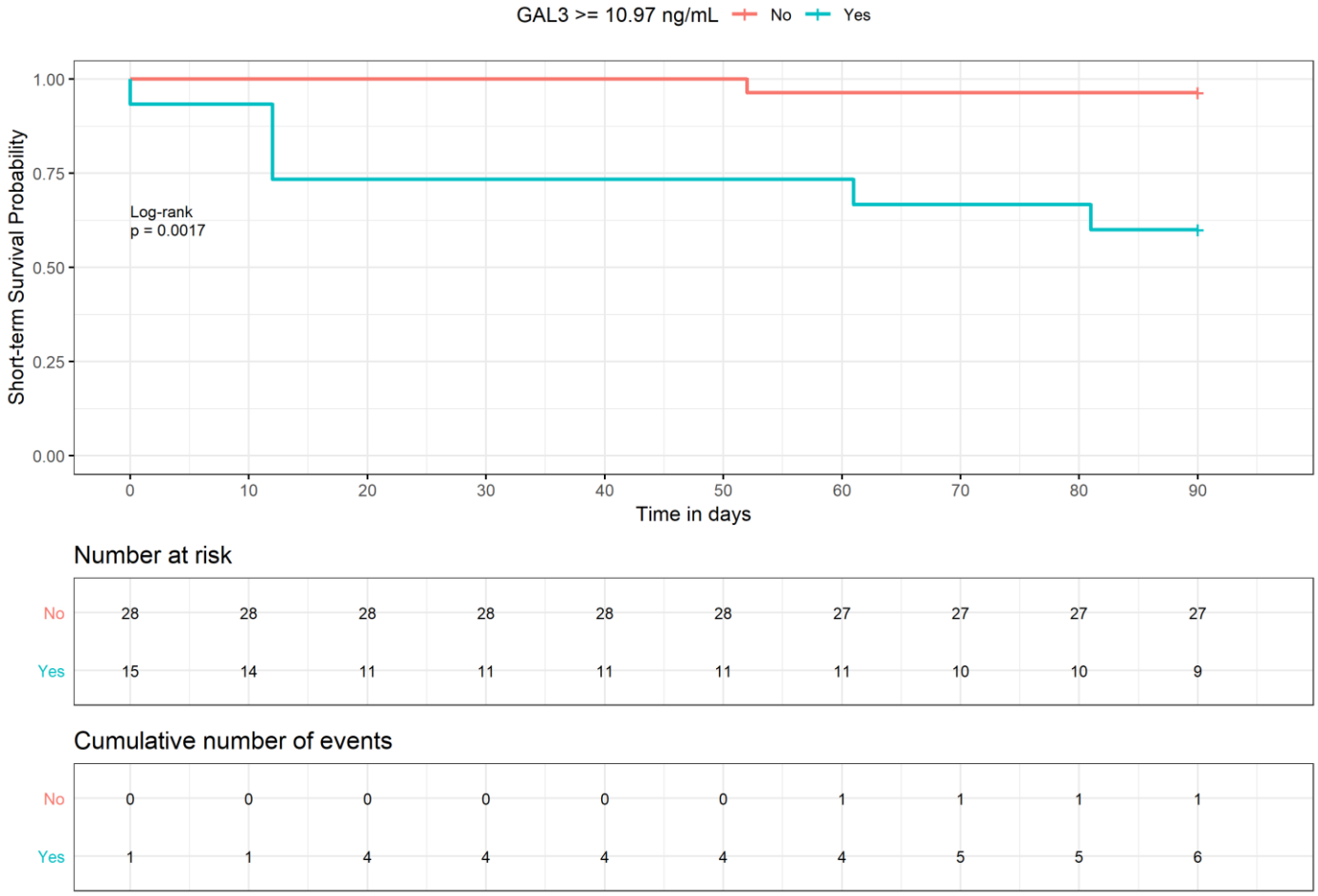

Figure 18 - Short-term mortality - Kaplan Meier: GAL3 ≥10.97 ng/mL

The **combination of Gal-3 ≥11.41 ng/mL and admission NT-proBNP ≥1800 ng/L represented an increased risk of short-term mortality 18.8 times greater** (HR: 18.837, 95% CI: 2.193-161.811, P-value=0.007).

Relatively to long-term survival, the median Gal-3 value was 9.24 (6.80-10.37) ng/mL in the group that survived compared to 11.36 (9.99-12.59) ng/mL in the deceased. This difference between groups was significant (P-value=0.029).

Supplementary univariate Cox proportional hazard model added that serum **determinations of Gal-3 ≥9.9 ng/mL increased long-term mortality 4.5 times** (HR: 4.492, 95% CI: 1.594-12.656, P-value=0.004).

The long-term mortality Kaplan Meier curve for levels of Gal-3 ≥9.9 ng/mL is exemplified in Figure 19.

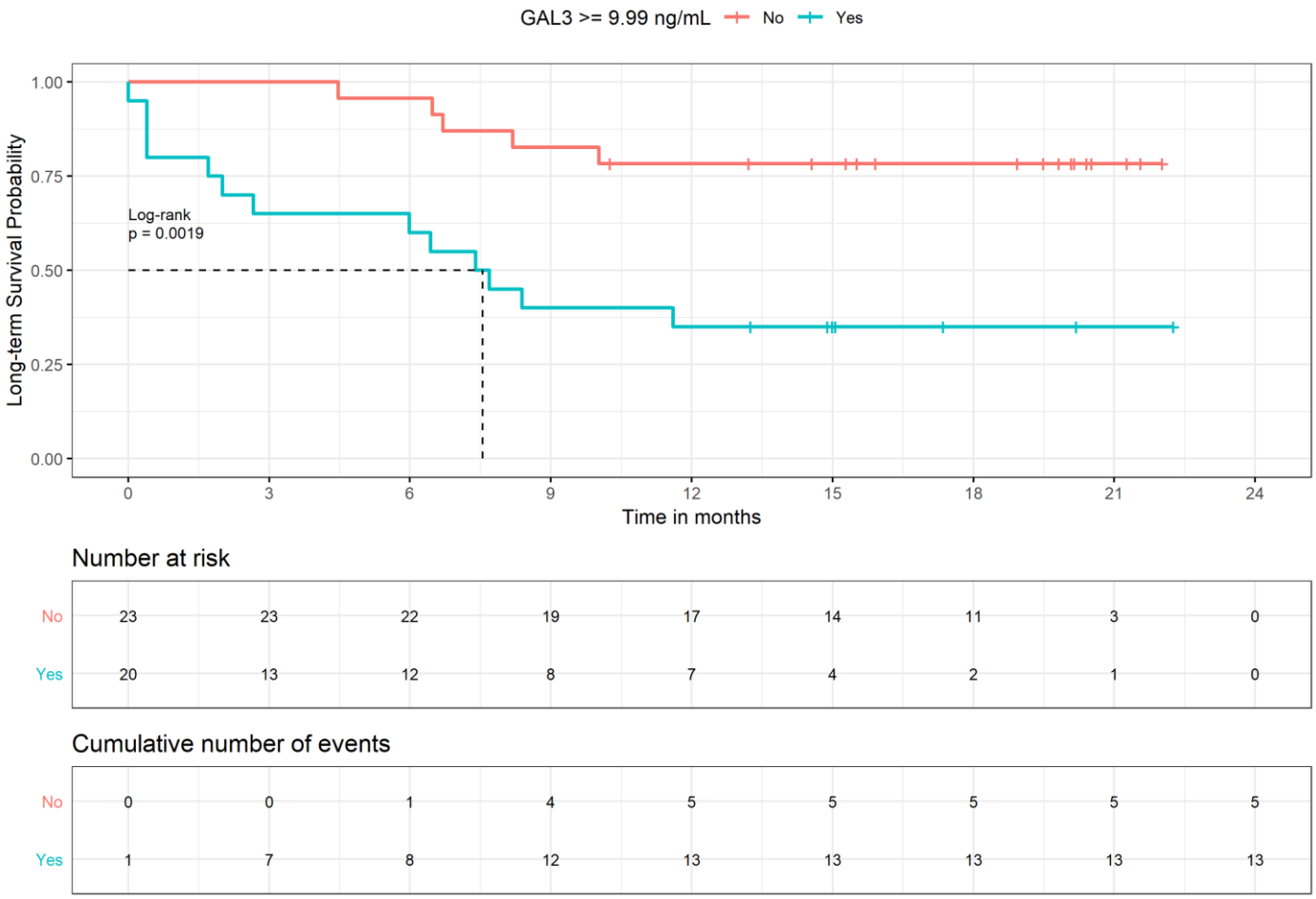

Figure 19 - Long-term mortality - Kaplan Meier: GAL3 ≥9.99 ng/mL

For **determinations of Gal-3 ≥10.97 ng/mL added to determinations of admission NT-proBNP ≥21336 ng/L the same outcome presented an incremented risk of 78 times** (HR: 78.025, 95% CI: 7.592-801.926, P-value<0.001).

Subgroup interpretation indicated that serum concentrations of Gal-3 ≥11.41 ng/mL increased long-term mortality 10.8 times for HFrEF patients (HR: 10.777, 95% CI: 1.181-98.303, P-value=0.035).

For Gal-3 ≥10.97 ng/mL and a cut-off of admission NT-proBNP ≥1800 ng/mL the HR was 13.5 (HR: 13.511, 95% CI: 1.415-129.012, P-value=0.024).

8.3.4. PRO-ADM

In our research a trend towards MR-proADM and NYHA functional class IV was perceived [MR-proADM median value of 4.2 (3.7 - 4.5) pg/mL for class IV patients compared to 3.2 (2.7 - 4.2) pg/mL in the class III group, P-value=0.081).

We point out that in the HFmrEF subgroup a trend towards MR-proADM and early readmission was identified (HR: 13.209, 95% CI: 0.378-461.525, P-value=0.155).

8.3.5. ST2

Spearman's correlation indicated a significant **negative relation between suppression of tumorigenicity 2 soluble receptor (sST2) levels and baseline GFR** (Coefficient: -0.418, P-value<0.001) **and admission GFR** (Coefficient: -0.438, P-value<0.001).

A trend towards sST2 levels and male patients was also identified using the same statistical method [median value 37.5 (20.6 - 47.9) pg/mL for the males compared to 25.0 (14.3 - 36.1) pg/mL for the female patients, P-value= 0.089].

Likewise NT-proBNP, **obese patients had lower amounts of sST2** [median 35.5 (22.3-46.4) pg/mL for non-obese versus 13.1 (10.1-23.4) pg/mL for the obese, P-value=0.001)].

We could not achieve a statistically significant link between sST2 and early mortality, when assessed isolatedly, although the subset of patients that survived had lower determinations that those who deceased [median 28.94 (14.40-42.52) pg/mL compared to 27.21 (23.81-54.50) pg/mL, respectively].

However the **combination of sST2 ≥24.78 pg/mL and Gal-3 ≥9.99 ng/mL determined an 8 times increased risk for early mortality** (HR: 8.108, 95% CI: 1.566-41.973, P-value=0.013).

In the HFpEF subgroup, gathering serum determinations of sST2 ≥24.78 pg/mL and Gal-3 ≥10.97 ng/mL resulted in a HR of 19.3 (HR: 19.332, 95% CI: 1.657-225.567, P-value=0.018).

Considering long-term mortality, elevated concentrations of sST2, were found to be a reliable predictor [median 22.33 (12.98-40.84) pg/mL in the group that survived compared to 35.47 (25.77-46.01) pg/mL in the group that died].

We recognized a **risk for long-term mortality of 4.9 times for levels of sST2 ≥24.78 pg/mL** (HR: 4.846, 95% CI: 1.396-16.825, P-value=0.013).

The long-term mortality Kaplan Meier curve for sST2 ≥24.78 pg/mL is depicted in Figure 20.

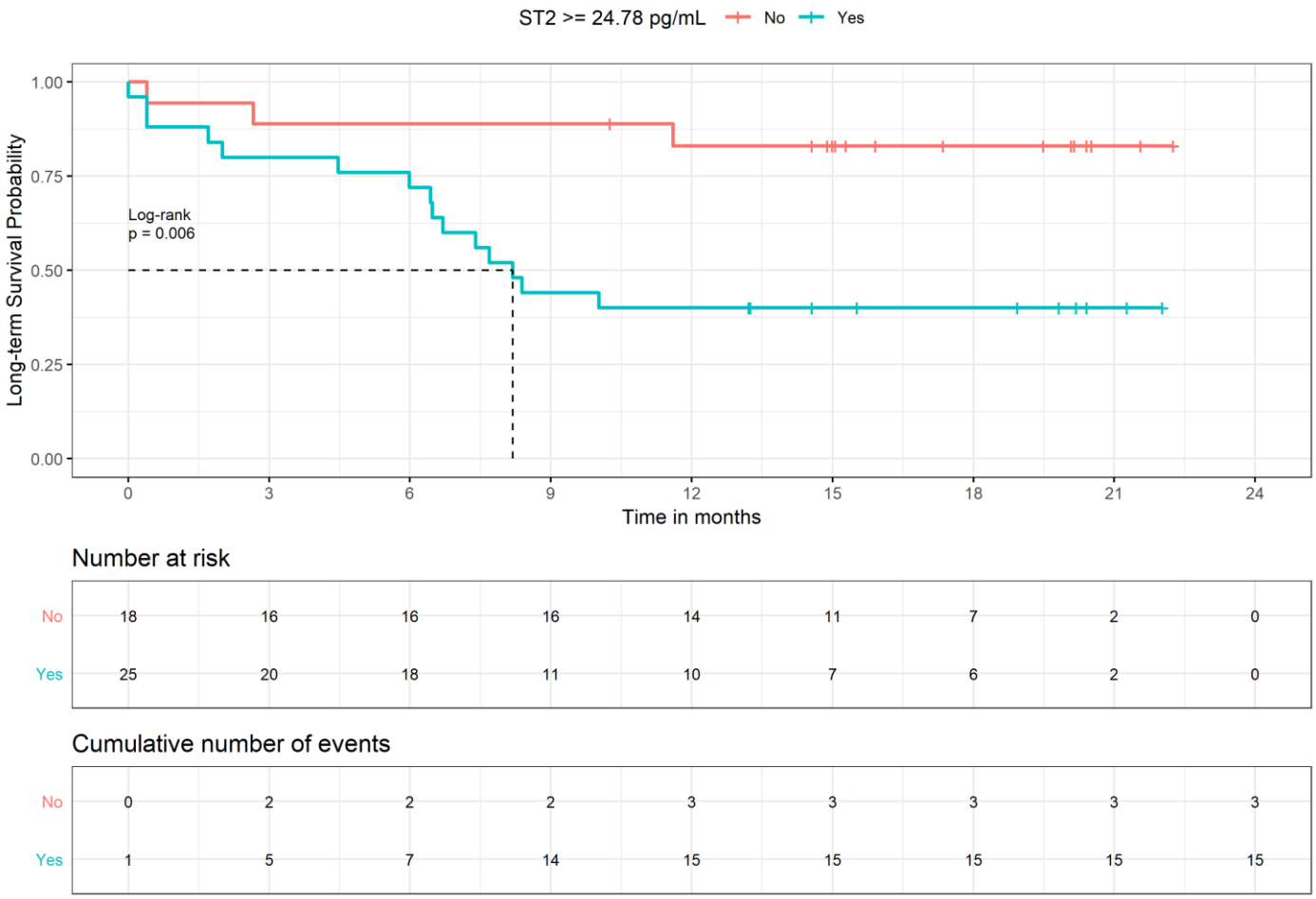

Figure 20 - Long-term mortality - Kaplan Meier: sST2 ≥24.78 pg/mL

Remarkably **for each increment of 10 pg/mL of sST2 the risk for long-term mortality elevated up to 37%** (HR: 1.372, 95% CI: 1.021-1.843, P-value=0.036).

Curiously, **if values of admission NT-proBNP ≥21336 ng/L were added to levels of sST2 ≥24.78 pg/mL the risk slightly augmented to 6 times** (HR: 5.953, 95% CI: 1.683-21.055, P-value=0.006) **and if, instead, values of Gal-3 ≥9.99 ng/mL were considered the risk increased roughly to the same extent** (HR: 6.209, 95% CI: 2.393-16.114, P-value<0.001).

For the HFrEF subgroup the long-term mortality risk for the combined values of sST2 ≥24.78 pg/mL and values of Gal-3 ≥9.99 ng/mL was highest (HR: 15.782, 95% CI: 1.593-156.322, P-value=0.018) compared to the general population and the HFpEF subgroup (HR: 5.2, 95% CI: 1.223-22.187, P-value=0.026).

For the HFpEF subgroup the long-term risk for the combined values of sST2 ≥24.78 pg/mL and admission NT-proBNP ≥1800 ng/L was 8.4 times higher (HR: 8.381, 95% CI: 1.003-70.037, P-value=0.05).

8.3.6. RECEIVER-OPERATOR CHARACTERISTIC (ROC) ANALYSIS

As specified earlier, to analyze the prognosis capabilities of each biomarker individually and in combination, we need to have specific prognostic cut-offs for each of the biomarkers.

Because there are no standardized cut-offs for these biomarkers, an assessment of the overall performance of each biomarker was performed using the multiclass AUCROC, as defined by Hand and Till, as a predictor of each of the events of interest. Taking into consideration the low number of subjects and samples, it was decided to consider as relevant predictors biomarkers which have an AUCROC above 0.7 and in which the 95% confidence interval does not contain 0.5 (value for which the predictor makes random guesses).

For the "Early Rehospitalization" outcome, **the only biomarker with an acceptable AUCROC value was Galectin-3** (AUCROC: 0.74; CI95%: 0.55-0.92). For this biomarker, **the optimal cut-off value** (Youden Index) **was 11.41 ng/mL with a high Negative Predictive Value** (NPV: 0.93) indicating a good capability in predicting (**93% probability) that no early rehospitalization events occur if the biomarker is below the cut-off**. The Positive Predictive Value (PPV: 0.54) being able to predict the event with a probability of 54%.

Regarding the remaining biomarkers, hsTnT had an almost relevant AUCROC (0.67) but with 95% confidence intervals too wide (0.44-0.89), probably due to the low number of samples available.

For the "Early Death" outcome, **there were two biomarkers with acceptable AUCROC values**, **Galectin-3** (AUCROC: 0.85; CI95%: 0.74-0.97) **and NT-proBNP** (AUCROC: 0.75; CI95%: 0.58-0.92) **at admission** to hospitalization.

For Galectin-3, the optimal cut-off value (Youden Index) **was 10.98 ng/mL with a perfect Negative Predictive Value** (NPV: 1.0), indicating an excellent capability in predicting (**100% probability) that no early death events occur if the biomarker is below the cut-off**. Regarding the capability of predicting "Early Death" events, the biomarker has inferior capabilities (PPV: 0.44), but it is still relevant enough to take it into consideration, given the 44% probability of the event to occur.

For NT-proBNP at admission to hospitalization, the optimal cut-off value (Youden Index) **was 21336 ng/L with a high Negative Predictive Value** (NPV: **0.91**). The Positive Predictive Value (PPV: 0.64) was inferior, being able to predict with 64% probability an event of early death.

Regarding the remaining biomarkers, MR-proADM and NT-proBNP at the discharge of the hospitalization had almost relevant AUCROC values (0.65 and 0.68) but with 95% confidence intervals too wide (0.44-0.86 and 0.40-0.97), once more probably due to the low number of samples available.

For the "Long-term Death" outcome, we decided to consider two biomarkers with AUCROC slightly below 0.7, due to the fact that they have a significant behavior (95% confidence intervals are above 0.5).

For this outcome **there were three biomarkers with acceptable AUROC values**. **Galectin-3** (AUCROC: 0.69; CI95%: 0.52-0.86), **ST2** (AUCROC: 0.69; CI95%: 0.53-0.85) **and hsTnT** (AUCROC: 0.77; CI95%: 0.57-0.97).

For Galectin-3, the optimal cut-off value (Youden Index) **was 9.99 ng/mL with a Negative Predictive Value of 0.78 and Positive Predictive Value of 0.65.**

The **ST2** biomarker has similar capabilities to Galectin-3**, with an optimal cut-off value** (Youden Index) **of 24.79 pg/mL with Negative Predictive Value of 0.83 and Positive Predictive Value of 0.60.**

The biomarker with best results for predicting long-term mortality was hsTnT. **The optimal cut-off value** (Youden Index) **was 52 ng/L with a Negative Predictive Value of 0.85 and Positive Predictive Value of 0.62**.

Regarding the remaining biomarkers, NT-proBNP at admission to hospitalization was almost significant (AUCROC: 0.65; CI95%: 0.49-0.79).

Characteristics	Patients (n=65)	Characteristics	Patients (n=65)
Age, mean (SD)	79.2 ± 10.8	**LVEF, mean (SD)**	50.38 ± 19.07
Female Gender, n (%)	37 (56.9)	**Systolic Blood Pressure (Admission), median**	145.0 (121 - 163)
Hypertension, n (%)	58 (89.2)	**Diastolic Blood Pressure (Admission), median**	77.0 (65 - 89)
Type 2 Diabetes, n (%)	25 (38.5)	**GFR (Baseline), median**	57.8 (43.8 - 82.2)
Dyslipidemia, n (%)	41 (63.1)	**GFR (Admission), median**	47.9 (33.2 - 68.1)
Obesity, n (%)	17 (26.2)	**Urea (Baseline), median**	47.0 (35 - 76)
Atrial Fibrillation, n (%)	28 (43.1)	**Urea (Admission), median**	64.0 (38 - 97)
Family History of CVD, n (%)	31 (47.7)	**Creatinine (Baseline), median**	1.0 (0.8 - 1.4)
Tabagism, n (%)	21 (32.3)	**Creatinine (Admission), median**	1.3 (1.0 - 1.8)
Chronic Kidney Disease, n (%)	34 (52.3)	**Cardiorenal Syndrome, n (%)**	35 (53.8)
Previous Acute Myocardial Infarction, n (%)	27 (41.5)	**Hemoglobin, mean (SD)**	11.7 ± 1.9
Hypertensive Cardiomyopathy, n (%)	44 (67.7)	**Red Blood Cell Distribution Width, median**	15.0 (13.8 - 16.2)
Ischemic Cardiomyopathy, n (%)	22 (33.8)	**Natremia, median**	138.0 (136 - 140)
Valvular Cardiomyopathy, n (%)	56 (86.2)	**Serum Iron, median**	40.1 (27.6 - 60.1)
NYHA class III, n (%)	43 (66.2)	**Serum Ferritin, median**	149.1 (52.3 - 350.9)

Transferrin Saturation, median	14.0 (10 - 21)	**Anemia, n (%)**	38 (58.5)
Total Iron-Binding Capacity, mean (SD)	281.5 ± 76.1	**Iron Deficiency, n (%)**	30 (46.2)
Absolute Iron Deficiency, n (%)	20 (30.1)	**Functional Iron Deficiency, n (%)**	10 (15.4)
Anemia with Iron Deficiency, n (%)	17 (26.2)	**Anemia without Iron Deficiency, n (%)**	15 (23.0)
Iron Deficiency without Anemia, n (%)	13 (20.0)	**Absolute Iron Deficiency without Anemia, n (%)**	6 (9.2)
FT4, mean (SD)	1.19 ± 0.25	**Functional Iron Deficiency without Anemia, n (%)**	7 (10.8)
NT-proBNP (Admission), median	5701.0 (1867 - 11961)	**ACE Inhibitor, n (%)**	43 (66.2)
NT-proBNP (Discharge), median	2837.0 (520 - 5085)	**Beta Blocker, n (%)**	38 (58.5)
hsTnT, median	51.0 (31 - 117)	**Mineralocorticoid Receptor Antagonists n (%)**	19 (29.2)
Galectin-3, median	9.82 (7.94 -12.00)	**Angiotensin II Receptor Blocker, n (%)**	11 (16.9)
ST2, median	27.22 (15.45-44.39)	**Loop Diuretic, n (%)**	54 (83.1)
Mid-Regional Pro-Adrenomedullin, mean (SD)	4.12 ± 0.95	**Digoxin, n (%)**	8 (12.3)
Erythropoietin, median	14.89 (9.86 - 22.65)	**Left Ventricular Diastolic Diameter (LVDD), median**	53.0 (47 - 59)
Pulmonary Artery Systolic Pressure (PSAP), median	34.60 (25.94 - 50.05)	**Tricuspid Annulus Plane Systolic excursion (TAPSE), mean (SD)**	17.7 ± 4.0
Left Ventricular Systolic Diameter (LVSD), median	36.0 (19 - 78)	**Inferior Vena Cava Inspiratory Collapse (no), n (%)**	9 (13.8)

Values are median (IQR), n (%), or mean ± SD.

Table 2 - Baseline characteristics

9. DISCUSSION

This study confirmed the high early readmission rate of HF patients, as 33.8% of the population was rehospitalized within 90 days post-discharge. This readmission cypher is in accordance with the EPICA study which estimated a 20 to 30% readmission hazard for the referred period of time.[14,15]

The 30 day readmission rate was 15.4%, also in accordance with national data.[25]

The 30 day mortality rate was 10.8% similar to 11.75% found in the Multinational Observational Cohort on Acute Heart Failure (MOCA) study.[53]

We identified a 90 day mortality rate of 18.5%. Even though we excluded patients with active cancer, who have an elevated mortality, we registered a high percentage of death, slightly above some series,[8] which reflects the severity of the clinical cases that we enrolled.

The year mortality was 36.9%, above the 30% registry of the British National Heart Failure Audit.[20]

At the end of the follow-up 40% of the patients had deceased reflecting the severity of the HF syndrome.

We believe that these findings corroborate the assumption that HF has a tremendous social and economic impact.

Plenty clinical, hemodynamical, laboratorial and imagiological findings have been linked to the outcome of HF.

Yet, given the complexity of the disease and multiple comorbidities that surround it, one should not rely on a solo indicator to estimate prognosis.

Although some predictors correlate with HF outcome in a statistical and epidemiological basis, a single predictor may not be trustworthy to guide the therapy of an individual patient.

The confluence of as many well established predictors of survival as possible seems to be the most accurate mean to assess the outcome.

Some predictive models combine different prognosticators to estimate HF prognosis.[54, 55, 56]

However, these models are based on the analysis of a specific subset of patients and as new therapies emerge and guidelines are updated they become archaic, and first and foremost, clinical judgment is the essence of the art of making Medicine and shall never be replaced by a statistical model.

Therefore such prognostic models should be used as a tool to help estimate more accurately the outcome of HF patients.

The evolution of decompensated HF depends on multiple factors, namely its severity *per se*, its cause, the patient's characteristics, therapeutics and follow-up.

Despite its severity and chronicity, it is thought that more than half the readmissions for HF are preventable.[57]

The influence of the mentioned topics in the prognosis of the given population study will be scrutinized as follows.

9.1. DISEASE RELATED DETERMINANTS

The diverging mortality rates among series reflect, essentially, different disease severity of the enrolled patients.

Most of the data relative to survival come from systolic HF trials, since the information form diastolic HF is scarce.

The length of stay for HF patients is estimated to be between four to five days in the mild cases and around nine days in the more severe presentations.[58, 59]

Relying on recent Portuguese Health System official data, HF as the primary diagnosis represents the second highest hospital burden, being responsible for 182 512 hospitalization days corresponding to 18 588 patients, with a mean hospital stay of 9.8 days and an in-hospital mortality of 12.5%.[23]

In our study the mean hospital stay was 8.3 days.

We acknowledged a relation between the accumulated length of stay and early readmission, and subgroup analysis showed that the risk was highest for the HFrEF subgroup.

A trend towards the accumulated length of stay and, both, short and long-term mortality was also identified.

Subgroup analysis confirmed a consistent link between the accumulated length of stay and long-term mortality in the HFpEF.

In the same subgroup the length of stay per specific HF hospitalization was a predictor of impaired long-term survival.

While in the HFrEF subgroup, a trend towards the length of stay for a given HF hospitalization and early readmission was verified.

The number of hospitalizations correlated with short-term readmission in the overall population and in the HFmrEF subgroup and a trend towards greater risk in the HFpEF and the HFrEF subgroups was noted.

A trend-towards the number of hospitalizations and long-term mortality, nearly reaching statistical significance, was verified in the HFrEF subgroup.

Based on these findings, one can assume that the requirement for hospitalization is a relevant predictor of poor outcome as it reflects more severe disease and that patients hospitalized longer or repeatedly face a worse outcome.

Our impression finds support in an analysis that studied patients with reduced or preserved LVEF from the Candesartan in Heart failure: Assessment of Reduction in Mortality and Morbidity (CHARM) program, which established an association between longer hospitalizations and nonfatal admissions with subsequent mortality rates.[60]

Reynolds et al., suggested that the length of stay could be a proxy for the severity of HF since this parameter was related with readmission and mortality within 30 days and 1 year independently of comorbidities and CV risk factors.[61]

Solomon and collaborators, verified an increase in mortality risk after each hospitalization, and the risk was highest after the first month of discharge decreasing progressively over time. [60]

The onset of HF has a major influence on the outcome. As per the EuroHeart Failure Survey II the overall mortality was 6.7%, ranging from 5.8% in CHF decompensated patients to 8.1% in *de novo* cases.[58]

In our study such comparison could not be made since all HF admissions were due to CHF decompensation given to the fact that acute coronary syndromes are the most frequent cause of *de novo* acute decompensated heart failure (ADHF)[2] and ST-elevation acute coronary syndromes are routinely admitted to Cardiology ward in order to perform percutaneous transluminal coronary angioplasty and to recover, afterwards, in coronary care units, while non-ST-elevation acute coronary syndromes are often admitted to Internal Medicine ward.

9.1.1. ETIOLOGY

It is consentaneously assumed that prognosis is inherently related to the underlying cause of HF.

In the subgroup of patients suffering from HFrEF, a trend towards ischemic cardiomyopathy and early readmission and another trend towards long-term mortality were documented.

Ischemic cardiomyopathy connotes with a worse prognosis than other common causes of HF.

This fact has been documented for more than two decades ago.[62, 63]

In one study the etiology of cardiomyopathy was a relevant predictor of outcome, since the course of HF varied with its cause. For instance, ischemic cardiomyopathy patients had worse prognosis than those with hypertensive cardiomyopathy. Peripartum cardiomyopathy, a more benign and potentially reversible condition, had the best outcome.[64]

Interestingly a study performed in Brazil found that Chagas disease, a rare cause of HF in the western world, evolved with worse prognosis than other forms of HF.[65]

9.1.2. LEFT VENTRICULAR EJECTION FRACTION

A, 2016, systematic review by Van Riet et al., suggested that the 'epidemic' of HF seems to be altering, since the prevalence of diastolic dysfunction is rising and currently superior to that of systolic dysfunction. The prevalence of the latter appears to have declined in the last century.[66]

In our study LVEF was a predictor of long-term mortality in the patients with HFrEF, as per increments of 10% of LVEF a risk reduction of 65.2% was found.

Moreover, a trend towards short-term readmission and LVEF and another trend towards short-term survival and LVEF were, also, present in the referred subgroup.

Several major trials achieved similar conclusions.

The Valsartan heart failure trial (Val-HeFT) revealed an association between LVEF and mortality.[67]

The LVEF was inversely proportional to mortality, as patients with mean LVEF of 17% had a 23 month all-cause mortality of 26% compared to those with an average LVEF of 35%, which had a 14% mortality for the same period of time. [67]

This assumption was corroborated by the Studies of Left Ventricular Dysfunction (SOLVD) trials.[68]

A retrospective analysis from the CHARM trials suggested that compromised LVEF was a powerful independent predictor of mortality and HF hospitalization.[69]

Normally, HF due to systolic dysfunction becomes clinically evident when LVEF falls below the 35-40%.

Nonetheless there is no accurate relation between clinical status and LVEF, as some patients with LVEF inferior to the above mentioned threshold are asymptomatic while others with higher LVEF refer symptoms.

In our study the mean (SD) LVEF in the HFrEF was 26.91 ± 8.91 %.

Gradman A et al., recognized that LVEF inferior to 20% is traditionally a marker of bad prognosis.[70]

Heart failure with borderline EF was first described, in 2013, in the ACA/AHA guidelines as the presence of HF symptoms and LVEF between 41% and 49%.[41]

In 2016, the ESC guidelines introduced a new concept for HF patients with LVEF between 40% and 49%, "heart failure with mid-range ejection fraction".[1]

This population is formed by patients with mild systolic dysfunction, but with characteristics of diastolic dysfunction.[1]

Therefore, patients are classified according to baseline LVEF into HFrEF (EF <40%), HFmrEF (EF between 40-50%) and HFpEF (EF ≥50%).[1]

In our study we stratified the population following the above mentioned criteria.

Hsu et al., raise the question that HFmrEF could be a transition stage between HFpEF and HFrEF, rather than a distinct clinical entity.

Albeit there are effective, guideline-directed therapies for HFrEF, therapies that objectively change the course of HFpEF and HFmrEF lack scientific support. [71]

9.1.3. NYHA FUNCTIONAL CLASS

It has been proven that greater NYHA functional class patients evolve with worse prognosis since the late eighties.[72, 73]

The European Society of Cardiology Heart Failure Long-Term Registry confirmed that NYHA class III/IV status predicted mortality in all LVEF groups.[74]

Unfortunately, in our study we could not reach such conclusions most likely because of the limited participants enrolled.

The fact that the selected population was in some way homogenous, given that only severe cases were included, impeding the comparison with mild and moderate cases, as conducted in other trials, could also contribute to this matter.

9.1.4. REDUCED RIGHT VENTRICULAR FUNCTION

Although right ventricular function has a deleterious impact on HF prognosis, its assessment is often neglected, given the primordial role of the LV.

Aronson and colleges associated pulmonary hypertension and right ventricular dysfunction, often seen in concomitance, to adverse outcome in patients with chronic heart failure.[75]

Tricuspid annulus plane systolic excursion <18 mm, which suggests right ventricular failure, has been connoted with poor CV outcome, namely death.[76]

In our study a trend towards TAPSE and long-term mortality was detected and the mean TAPSE of the group of the patients that died was 17 mm.

A trend towards elevated PASP and long-term mortality was also verified and the median value in the group of patients who died was 45.00 (30.60-54.34) mmHg.

The absence of inferior vena cava inspiratory collapse, a well-known parameter of right ventricular overload, was a powerful predictor of both short and long-term mortality.

According to some authors the lack of inspiratory collapse of the inferior vena cava during the decompensation phase corresponded to a subgroup of patients with impaired long-term survival.[77]

The sum of these results leads us to believe that despite the undisputed role of LV function, the evaluation of the right ventricle can add relevant information to define HF prognosis.

Furthermore clinical signs of right-sided HF, discussed ahead, correlated with worse prognosis.

9.1.5. OTHER ECOGRAPHIC FINDINGS

In our study LV end-diastolic volume was a predictor of, both, short and long- term mortality.

The Val-HeFT investigators hold that LV dilation or an LV end-diastolic volume index >120 ml/m^2, which are parameters that suggest LV systolic dysfunction,[67] are determinants of worse outcome.

9.1.6. REFRACTORY SIGNS OF CONGESTION

Refractory signs of congestion are indicative of lack of response to diuretics, a marker of reduced tissue perfusion and poorer outcome.[78]

Hepatomegaly, a clinical sign of congestive hepatopathy, which ultimately can progress to cardiac cirrhosis (hepatic fibrosis due to right-sided HF) was a predictor of short and long-term mortality.

9.1.7. THERAPEUTICS

Neurohumoral blockers represent a breakthrough in HF management as they have changed the course of the disease by effectively reducing mortality, readmission rates and ultimately warranting a better quality of life for CHF patients.[79]

The SOLVD investigators realized that 90% of deaths in CHF patients are cardiovascular.[72]

The major causes of death in HF patients are progressive pump failure, which can be defined as continuous hemodynamic deterioration, due to cardiac malfunction, leading to death, and arrhythmic or sudden death, described as death within one hour of the onset of cardiovascular collapse in a previously stable patient. [72, 73]

The milestone drugs in HF treatment, ACE inhibitors, beta blockers (BB) and mineralocorticoid receptor antagonist (MRA), have irrefutable impact on both mortality and hospitalization, although through different mechanisms.

While ACE inhibitors improve cardiovascular burden mainly by preventing progressive myocardial dysfunction,[72,73] BBs[80] and MRAs[81] reduce both sudden cardiac death and death derived from progressive pump failure.

Faith is deposited in the new drug valsartan/sacubitril, which reduced the composite endpoint of cardiovascular death or HF hospitalization significantly, by 20%, in symptomatic patients with HFrEF tolerating an adequate dose of either ACE inhibitor or angiotensin receptor blocker (ARB).[82]

Kfoury et al., found a beneficial relationship between adherence to treatment and one-year survival.[83]

The British National Heart Failure Audit confirmed that post-discharge mortality at one year correlated to administration of disease-modifying drugs for HFrEF.[20]

The greatest benefit was achieved in patients leaving hospital medicated with ACE inhibitors, ARBs, BBs and MRAs.[20]

We were only capable of identifying a trend towards ACE inhibitor use and long-term mortality in the general population study and in the HFmrEF subgroup.

Lack of adherence to treatment (lifestyle modification and drugs) is a major issue in chronic diseases, particularly in HF.[84]

Michalsen A et al. argue that it is the most frequent cause of readmission due to HF, being responsible for 41% of the cases. The same series found that 12% of the readmitted patients where undertreated.[84]

Baretto and colleges concluded that considering that the main culprit of hospitalizations is inappropriate treatment, whether non-compliance or non-optimization, more assertive health care strategies combined to an effective treatment could result in an improvement of HF patients' wellbeing and decrease hospital costs.[65]

Compliance to standard of care measures plays an essential role in post-discharge outcome.

9.2. HIGH RISK PATIENTS' PROFILE

9.2.1. NON MODIFIABLE CARDIOVASCULAR RISK FACTORS

Concerning patient characteristics, advanced age and the male gender appear as risk factors for hospital readmission, in studies carried out in Europe[85] and in the USA[31].

There is a consistent link between increased readmission rates with age, since older patients are prone to more severe clinical conditions and suffer from a larger range of comorbidities. As a matter of fact morbidities and functional impairment are pointed as risk factors for rehospitalization in the elder.[86]

The Framingham Heart Study has proven more than two decades ago that mortality is proportional to advancing age.[87]

Modern HF trials, namely a post-hoc analysis from the CHARM study, have also demonstrated a significant relation between advanced age and all-cause mortality, after adjusting for known predictors of CV outcome. The risk augmented gradually with age and peaked at older groups.[88]

Lately, the European Society of Cardiology Heart Failure Long-Term Registry verified that advanced age predicted mortality in all LVEF groups.[74]

In a Portuguese study revising all-cause readmissions the incidence of rehospitalization did not vary with age among adult patients, nevertheless older patients (≥ 65) had an increased mortality (18.2% *vs.*10.6% in the 45-64 year old interval).[28]

The present study was composed by a very uniform population in terms of age which prevented inferences. Nevertheless, a trend towards compromised short-term survival and age ≥ 90 years was noted in HFpEF.

Albeit the comparison among distinct age groups did not show significant differences, the fact that in this aging population almost half of the patients died during follow-up, fundaments the impression that in CHF mortality is inherently related to advanced age.

The variation of readmissions with gender can be explained by the fact that, when compared to women the same age, the males have more severe clinical issues and greater mortality.[85]

According to national data, in the particular case of HF, male patients show a greater risk of readmission.[28]

The Framingham Heart Study found that women have better prognosis than men. Median survival after HF diagnosis was 3.2 years for women and 1.7 years for men. After 5 years only 38% of female patients were alive and 75% of men had deceased.

Curiously if only the subset of patients who survived the first 90 days were considered, survival rate rose up to 53% in women and 35% in men.[87]

This finding supports our assumption that the first 90 days post-discharge are critical in HF management.

The Cardiac Insufficiency Bisoprolol Study (CIBIS II) trial proved that regardless of BB treatment and baseline clinical profile, female gender is a significant independent predictor of survival in patients with CHF.[89]

Another analysis from the CHARM program showed that women have better fatal and nonfatal cardiovascular outcome than men.[90]

In our study 32.4% of women were readmitted preciously versus 35.7% of men.

Short-term mortality was similar between genders (18.9% for the females versus 17.9% for the males) but men showed a greater percentage of long-term death (42.9% versus 37.8%).

There is conflicting evidence whether race plays a role in HF outcome.

According to post-hoc analysis from the SOLVD trial black patients presented with higher mortality [91, 92] while in a post-hoc analysis from the Digitalis Investigation Group (DIG) trial mortality rates were similar between blacks and caucasians.[93]

In our study no difference in outcome regarding to race was observed, however one should be cautious to extrapolate such findings given that the participants were almost entirely caucasian.

9.2.2. MODIFIABLE CARDIOVASCULAR RISK FACTORS - THE METABOLIC SYNDROME

In 1988, Reaven described a triad of CV risk factors formed by arterial hypertension, diabetes and dyslipidemia, and designated it insulin resistance syndrome.[94]

In 1998, the WHO completed the constellation of CV risk factors by adding obesity and microalbuminuria, naming it metabolic syndrome.[95]

The progressive improvement in HF outcome is owed to the advance of the treatment of the disease (the continuous arrival of new drugs and devices and constant review of the guidelines), but also to concomitant improvement of the management of the underlying causes and cardiovascular risk factors.

Considering that metabolic disorders are in the genesis of CV diseases, it is plain to see that it is crucial to control these modifiable risk factors, in order to abrogate the CV risk *continuum*.

In our trial a trend towards the number of comorbidities and short-term readmission in the general population study and in the HFpEF group was identified.

Furthermore, we acknowledged a trend towards the number of comorbidities and short-term mortality in the HFrEF subset of patients.

Cardiovascular disease is responsible for 4 million deaths in Europe each year.[96]

Cardiovascular diseases represent the major cause of morbidity and mortality in the western world and are in *crescendo* in developing countries, and are also outlined as the main cause of hospital readmission. [31]

The VALSIM study, a landmark study that addressed the metabolic syndrome´s impact in Portugal, recognized a 27.5% overall prevalence.[97]

Adding to this matter, according to national epidemiologic studies, 24% of the population smokes.[98]

In our study 32.3% of the population were active smokers or had a tabagism past.

Furthermore, Isabel do Carmo and colleges, acknowledged that Portugal registers one of fastest growing rates of overweight and obesity in Europe, affecting 53% of the population between 18-64 years of age.[99]

The PREVADIAB study documented an astonishing cipher of three million Portuguese suffering from diabetes or impaired glucose metabolism.[100]

We verified a 38.5% prevalence of diabetics in the enrolled population.

The PHYSA study revealed that 42.2% of the Portuguese adult population is hypertensive,[101] in accordance with the 30-45% prevalence estimated in European registries[44].

Importantly, 74.9% of Portuguese hypertensive patients are treated and, only, 42.5% are controlled.

The average daily consumption of salt is 10.7 g, way above the recommended 5.8 g.[101]

In our study a remarkable 89.2% of hypertensive patients were identified.

This remarkable prevalence of arterial hypertension mimics the EPICA findings that arterial hypertension is the most frequent risk factor in HF patients.[14]

Concerning dyslipidemia, relying on WHO data, the prevalence of elevated total cholesterol was highest in Europe (54% for both sexes).[102]

The VALSIM study documented a 46.06% prevalence of dyslipidemia in Portugal.[97]

We found a 63.1% prevalence of dyslipidemia in our study.

Importantly, we recognized a trend towards dyslipidemia and risk of early readmission in the subset of patients with HFrEF.

Besides, a trend towards long-term mortality and dyslipidemia was also identified in the HFmrEF group.

From the exposed CV risks**,** diabetes stands out as a contributor to aggravate HF prognosis.

Diabetes alone can induce myocardial strain resulting in both systolic and diastolic ventricular dysfunction, in the absence of other possible etiologies, the so called "diabetic cardiomyopathy".[103]

A retrospective analysis from the CHARM program, which reviewed the prognostic value of several variables, revealed that diabetes was an independent risk factor for all-cause mortality and HF admissions in patients with ischemic cardiomyopathy.[69]

Data from the SOLVD trials confirmed that among patients with HF, the diabetic had higher mortality rates and were significantly more expected to be admitted for HF (risk ratio 1.6).[104]

We found a trend towards long-term mortality and diabetes, limited to the ischemic cardiomyopathy subgroup, likewise the SOLVD trial that confirmed an increase in all-cause mortality linked to diabetes, also, restricted to patients with ischemic cardiomyopathy (adjusted relative risk 1.37 compared to 0.98 in patients with non-ischemic cardiomyopathy). In the presence of coronary disease, diabetes presented as an independent predictor of worse outcome and was third in order of significance, after age and LVEF.[105]

It is thoroughly known that obesity is an independent risk factor for cardiovascular disease, nevertheless relying on data from The Acute Decompensated Heart Failure National Registry (ADHERE), obesity is not responsible itself for HF death.[106]

Horwich et al., in a large cohort of patients with advanced HF of multiple etiologies, realized that obesity was not linked to increased mortality and, surprisingly, could assure a more favorable prognosis.[107]

The percentage of obesity in our population study was 26.2%.

The CHARM investigators found that lower BMI was associated with a greater risk of cardiovascular death and non-cardiovascular death than BMI ranging from 30-34.9 kg/m^2.[108]

A lower BMI was independently related with mortality in HFrEF and HFpEF patients in the European Society of Cardiology Heart Failure Long-Term Registry.[74]

In parallel with the described studies, in our investigation obesity was not a risk factor for worse CV outcome, better off, a trend towards improved long-term survival was perceived.

A trend towards improved short-term survival and higher BMI was, as well, identified in the HFpEF subgroup.

Underweight could be a consequence of more severe disease, namely cardiac cachexia which, notoriously, evolves with poor prognosis.

9.2.3. OTHER RISK FACTORS

The ADHERE Registry followed more than 65 000 patients from several hospitals throughout the USA.[59]

This study was able to establish a risk stratification of HF patients based on ordinary evaluation data.

Urea levels >86 mg/dL, creatinine levels >2.75 mg/dL and systolic blood pressure <115 mmHg where consistent markers of poor outcome.

According to this stratification low risk patients had a 2.2 % mortality percentage while the high risk group had a 20.9% mortality rate.

9.2.3.1. Blood Pressure

Low blood pressure plays a role in HF outcome as it is a clinical sign of lack of tissue perfusion and more severe disease.

Decreased systolic, diastolic and mean blood pressure values correlate to reduced survival.

A post-hoc analysis of the DIG trial established a trend towards increased mortality in patients with systolic blood pressure <100 mmHg and diastolic blood pressure <60 mmHg.[109]

In the SOLVD study, each 10 mmHg decrease in baseline mean arterial pressure was associated with a 14% increase in global and cardiovascular mortality.[110]

The European Society of Cardiology Heart Failure Long-Term Registry concluded that low systolic blood pressure was a predictor for mortality in HFrEF and HFmrEF patients.[74]

Our results consubstantiate these milestone studies as systolic blood pressure was a prognosticator of short-term mortality. Besides, systolic blood pressure <100 mmHg increased short-term mortality risk more than 5 times.

In resemblance with the exposed data, we found a link between systolic blood pressure and long-term mortality. Comparatively to short-term mortality, the risk declined along follow-up.

As anticipated, the HFrEF subgroup presented the highest hazard for long-term mortality.

Regarding diastolic blood pressure it was also a predictor of short-term mortality and for values of diastolic blood pressure <60 mmHg the risk for short-term mortality increased 11.1 times in the HFrEF subgroup.

Diastolic blood pressure <60 mmHg was, also, a maker of worse long-term survival in the HFrEF subgroup, and, again, the risk was inferior to that of early mortality.

These results suggest that both short-term and long-term mortality risk related to low blood pressure is greatest in HFrEF patients.

Remarkably, the risk seems to decline after the crucial 90 days post-discharge.

9.2.3.2. Renal Function

Renal dysfunction also represents impaired tissue perfusion.

Major studies like the EuroHeart Failure Survey II and the ADHERE have established renal impairment as a marker of poor prognosis.[58, 59]

A systematic review stated that renal failure is a predictor of poor outcome since it implicates higher rates of mortality and hospitalization in patients with HF.[70]

Smaller trials have also been able to confirm this statement.[65]

The European Society of Cardiology Heart Failure Long-Term Registry verified that chronic kidney disease predicted mortality in all LVEF groups.[74]

In our study the patients with impaired renal function evolved with a worse prognosis as several renal function parameters correlated consistently with precocious readmission and all-cause mortality.

Based on our results one can infer that abnormal baseline values of urea and creatinine (which can represent CKD) correlated better with worse short-term readmission and short-term mortality prognostication than altered admission values (which could represent only acute kidney injury).

Subgroup analysis, corroborated this assumption given that in the HFrEF subgroup long-term mortality risk was greater with elevated baseline urea (HR=1.132) than with elevated admission urea (HR=1.105).

In what matters to long-term mortality the hazard was, plausibly, greater for admission GFR <15 ml/min than for GFR <30 ml/min.

As expected, for admission GFR <30 ml/min the risk for long-term mortality was inferior in the subgroup of HFpEF (HR=3.640) comparing to that of the general population (HR=3.906) and the risk for this end-point was also inferior considering admission creatinine for the given groups (HR=1.080 versus HR=1.104, respectively).

Subgroup analysis confirmed an expected worse outcome for short-term mortality in HFrEF patients, compared to general population study for similar increments of creatinine and for GFR <30 ml/min.

Coherently, long-term mortality risk was greatest, regarding admission creatinine and GFR <30 ml/min, in the HFrEF subgroup (HR=1.148 and HR=13.387, respectively).

Remarkably, the HFrEF benefited more from the increase in admission GFR than general population, in what matters to long-term survival. This finding suggests that HFrEF is a vulnerable subgroup in which renal function is a determinant marker of prognosis.

We believe that the fact that all the renal function parameters, customarily used in general practice, correlated consistently with the aimed end-points, adds valuable information concerning HF prognosis.

Furthermore, CKD was an important clinical prior as it correlated with short-term mortality (present in 45.3% of survivors versus 83.3% of the decedents) and cardiorenal syndrome was found to be a strong predictor of both short and long-term mortality. Once again, the long-term mortality hazard, related to cardiorenal syndrome was greatest in the HFrEF subgroup.

9.2.3.3. Atrial fibrillation

Atrial fibrillation and concomitant HF is very frequent.[111, 112]

In our population AF reached a remarkable prevalence of 43.1%.

There is some controversy relative to its prognostic significance since some studies point it as an independent mortality risk predictor while others do not.

A retrospective analysis of the SOLVD trials compared patients with AF to those in sinus rhythm, and concluded that AF, in patients with asymptomatic or symptomatic left ventricular systolic dysfunction is related with an increased risk for all-cause mortality.[112]

The authors presumed that AF is related with progressive left ventricular systolic dysfunction, implicating an increased risk for pump-failure death.[112]

A contemporary analysis of the Framingham cohort over 50 years, validated this presumption.[113]

Atrial fibrillation predicted mortality in HFpEF patients in the European Society of Cardiology Heart Failure Long-Term Registry.[74]

However, likewise, the Veterans Affairs Vasodilator-Heart Failure Trial (V-HeFT I and II) investigators that defended that AF does not increase major morbidity or mortality in CHF,[111] in our study no connection was acknowledged between AF and CV outcomes.

9.2.3.4. Bundle Branch Block

Left Bundle Branch Block is a common ECG finding in HF, present in about 25% of the patients as specified by some series.[114, 115]

In our study the percentage of LBBB (21.5%) was close to the available data.

Although it has been reported that QRS prolongation ≥120 msec, in HF patients, is associated with increased all-cause mortality[114, 115, 116] and even sudden death[114], there is conflicting data regarding its direct

impact on mortality, since some found it to be an independent risk factor for mortality[114] while others did not[115].

Such divergence raises the question whether LBBB is just a marker of worse outcome or a consistent and direct cause of mortality.

In our study LBBB was a marker of short-term mortality risk in the overall population study.

Regarding long-term survival, LBBB was also a predictor of worse outcome in the HFrEF subgroup.

Ventricular dyssynchrony as an effect of anomalous conduction could justify the adverse outcome.[114]

According to Mueller et al., RBBB is a powerful predictor of mortality in patients with ADHF, and so prompt recognition of this high-risk group could help to offer tailored treatment in order to improve the prognosis.[117]

We were able to detect a link between RBBB and early HF readmission in the general population study.

Pellicori et al., also document a worse outcome in HF patients with RBBB.

According to these authors patients with QRS ≥120 msec with RBBB morphology frequently have more severe bi-ventricular dysfunction.[118]

9.2.3.5. Hyponatremia

Hyponatremia results from a series of physiologic compensation mechanisms to balance the low output state patent in HF.

Hyponatremia is frequent in HF patients and is a recognized predictor of short-term outcomes in HF.[119]

Otherwise unexplained hyponatremia was associated to poor prognosis in a study that enrolled patients with severe HF, as patients with sodium <137 meq/L had less than half the median survival (164 Vs 373 days).[120]

An observational study from the Duke Databank for Cardiovascular Diseases evidenced that in HF patients with LV systolic dysfunction hyponatremia was independently linked to increased risk of all-cause mortality and cardiovascular mortality/rehospitalization.[119]

The cut-off of sodium <137 meq/L, increased early readmission hazard around 10 times in the HFmrEF subgroup, although, statistical significance was marginally missed (P-value=0.053).

9.2.3.6. Free Thyroxine

Hypothyroidism, defined as elevated serum values of thyroid stimulating hormone (TSH), associated to decreased levels of FT4 or free triiodothyronine (FT3) has been pointed as a risk factor of HF.

Thyroid hormones play an important role in cardiovascular homeostasis, as FT4 and FT3 favor inotropism and chronotropism, and also mediate diastolic function and systemic vascular resistance.[121]

Nevertheless, the mechanism by which hypothyroidism aggravates HF outcome needs clarification.

We recognized that HFmrEF patients with higher FT4 levels showed a decreased early readmission rate.

Subgroup analysis also identified that HFrEF patients with greater FT4 concentrations evolved with a better short-term survival.

Concerning long-term mortality, FT4 also had a protective role as in the general population study and in the HFrEF subgroup, those with higher values had a better prognosis.

Our results find fundament in a meta-analysis that included 13 articles, which acknowledged that these impaired thyroid hormones determined an increased risk of all-cause mortality, as well as hospitalization, in patients with HF.[122]

We believe that the recognition and treatment of risk factors that influence HF outcome, namely hypothyroidism, beyond HF specific therapy, may further contribute to ameliorate HF prognosis.

9.2.3.7. Anemia and Iron Deficiency

Mild anemia is a common condition in patients suffering from chronic diseases, of which HF is no exception.[123]

Moreover, a 2017 Portuguese study documented that anemia and iron deficiency are highly prevalent in older Portuguese adults, particularly amongst those over 80 years of age, affecting 31.4% and 42.8%, respectively, of the referred age group.[124]

Another 2017 Portuguese study addressing this topic, the PRO-IRON study, acknowledged that anemia and iron deficiency are extremely frequent conditions in patients admitted to Internal Medicine ward, and correlate with in-hospital mortality.[125]

We were able to confirm such high rates as 58.5% of the population studied had anemia and 46.2% had iron insufficiency.

In the particular case of ADHF, according to the available data, the prevalence of iron deficiency ranges from 50% to 80%. [126, 127, 128, 129]

Importantly, iron depletion in the setting of ADHF is predominantly absolute,[128, 129] as observed in our study.

Customarily, anemia results from depleted iron supplies and/or impaired transportation.[130]

Anemia complicating congestive HF is multifactorial, resulting from the combined effect of hemodilution compromised glomerular filtration rate, iron deficiency, inflammation.[130]

Nonetheless, HF, *per se*, promoting inflammatory response through cytokine production, is sustained by Silverberg and collaborators, as a potential mean of damaging the bone marrow and therefore provoking anemia.[131]

It has, also, been postulated that HF patients may develop iron deficiency due to the depletion of iron stores or defective iron absorption and limited availability of iron recycled in the reticuloendothelial system.[132, 126]

Although the inflammatory role of elevated hepcidin in HF, which inhibits iron absorption, has been hypothesized, recent studies found a rather low-hepcidin profile in HF patients.[133]

The available data establishes a connection between anemia and increased mortality in HF patients, nevertheless, it is not unanimous if it is a predictor of mortality or simply a marker of more severe HF.[133]

Anemia has also been related to an increased hospitalization risk.[134, 135]

The mechanism by which anemia aggravates HF prognosis is not clear, although it seems to be linked to increased myocardial workload.[136]

The pathophysiological pathway for progressive iron deficiency in both chronic and acute HF also lacks of clarification.[130]

It appears that HF contributes to myocardial iron depletion and, on the other hand, myocardial iron shortage aggravates HF, in a cyclic fashion.[137]

Our study confirmed that anemia was an independent risk factor for short-term rehospitalization and long-term mortality.

Sex thresholds, as described above, further increased the risk for short-term rehospitalization and long-term mortality.

Our findings support the idea that gender adjusted thresholds for anemia may be useful in the estimation of outcomes.

As anticipated, short-term readmission risk, resulting from anemia, was greater in the HFrEF group (HR=5.425) than in general population study.

Importantly, absolute iron deficiency determined an impressive 7.2 increased risk of short-term mortality in general population study, in addition, in the HFrEF subgroup elevated serum iron was a protective factor for short-term mortality.

We were able to link other indicators of iron kinetics to some of the proposed outcomes, since a trend towards total iron binding capacity (which is increased in iron shortage)[138] and early rehospitalization was detected.

Albeit customarily iron deficit has been considered to have clinical repercussion only in the presence of anemia, some trials proved that it is advantageous to treat iron deficiency in both patients with anemia and without anemia.

A randomized controlled trial of 32 patients with moderate to severe CHF (NYHA class III and IV) with a LVEF ≤40%, despite maximally tolerated doses of CHF drugs and whose hemoglobin levels were between 10 and 11.5 g/dL, indicated that treating anemic patients to a hemoglobin goal of 12.5 g/dL, with subcutaneous erythropoietin and intravenous iron resulted in a global improvement of clinical and laboratorial profile and was connected with less hospitalization, renal impairment and less need for diuretics.[123]

The Ferric Carboxymaltose in Patients with Heart Failure and Iron Deficiency (FAIR-HF) trial comprised 459 ambulatory patients with CHF of NYHA functional class II or III, a LVEF of 40% or less (for patients

with NYHA class II) or 45% or less (for NYHA class III), iron deficiency (ferritin level <100 μg/L or between 100 and 299 μg/L, if the transferrin saturation was <20%), and a hemoglobin level of 95 to 135 g/L. The treatment arm was submitted to a 24 week intravenous ferric carboxymaltose regimen, either with or without anemia (defined as a hemoglobin level ≤120 g/L).

Along follow-up the intervention group improved symptoms, functional capacity, and the quality of life, leading the investigators to propose iron deficiency as a potential therapeutic target.

The rates of death and adverse events were similar in both arms.[139]

In a study that enrolled 35 CHF patients (with NYHA functional class II or III, ferritin <100 μg/L or between 100 μg/L and 300 μg/L with a transferrin saturation <20%; LVEF ≤45%) treated with intravenous iron, the authors recognized that in the intervention group, both anemic and non-anemic patients, benefited from improved exercise capacity and symptoms, nevertheless benefits were greater in anemic patients.[140]

A recent study recruited 60 patients with CHF (under optimal treatment), CKD and iron-deficiency anemia.

At six-month follow-up, the half of the study population that was treated with intravenous iron revealed an improvement of CHF symptoms (manifested as a statistically significant change in NYHA functional class) and renal function (both P-value <0.001 versus control).

Concerning biomarkers, the treated arm demonstrated a statistically significant reduction in NT-proBNP values at the end of the study.

Of note, the intervention group also showed a statistically significant increase in the LVEF and a reduction in the LV systolic diameter and LV diastolic diameter (P-value <0.01).[141]

The CONFIRM-HF trial (Beneficial Effects of Long-term Intravenous Iron Therapy with Ferric Carboxymaltose in Patients with Symptomatic Heart Failure and Iron Deficiency) was a multi-centre, placebo-controlled study that gathered 304 ambulatory symptomatic HF patients (nearly equal number of patients in NYHA class II and III), with compromised LVEF (≤45%), elevated natriuretic peptides, and iron deficiency (ferritin <100 μg/L or 100-300 μg/L if transferrin saturation <20%).

Treatment with ferric carboxymaltose, during one year, granted a significant reduction in the risk of HF hospitalizations and improved symptoms and quality of life, in both anemic and non-anemic patients.

However, no advantage was noted in relation to death hazard.[142]

A recent meta-analysis addressing intravenous iron therapy in iron-deficient patients with HFrEF confirmed a reduction in hospitalization rates and improvement in HF symptoms, exercise capacity and quality of life.[143]

The EFFECT-HF trial (Effect of Ferric Carboxymaltose on Exercise Capacity in Patients With Chronic Heart Failure and Iron Deficiency) compared the correction of iron deficiency, with intravenous ferric carboxymaltose, to standard of care, in a systolic HF population (LVEF ≤45%) with mild to moderate symptoms despite optimal treatment.

The investigators focused on peak oxygen consumption (peak VO2), considering that it is a reliable measure of exercise intolerance, and concluded that patients' global assessment and NYHA functional class improved in the treatment arm.[144]

Iron deficiency arises, not only as an independent prognostic marker, but also, as an interesting new treatment goal for symptom relief in selected HF patients.[130, 137]

The current ESC guidelines granted ferric carboxymaltose treatment in symptomatic patients with HFrEF and iron deficiency, both absolute and functional, in order to relieve symptoms, and improve exercise capacity and quality of life, a class IIA recommendation, based on A level of evidence.[1]

9.2.3.8. Red Cell Distribution Width

Red cell distribution width measures anisocytosis, which is the variability in size of the circulating erythrocytes.[145]

The major causes of anisocytosis are impaired erythrocyte production (such as deficiency of hematopoietic factors: iron, cobalamin and folate) and increased red cell destruction (namely hemolysis).[145]

Several conditions (e.g. inflammatory distress, chronic renal failure, nutritional deficiencies, hepatic congestion), very common in the HF population, compromise red cell balance.[145]

Therefore, although not specific, nor directly related to HF pathophysiology, this quotidian overlooked parameter seems to identify worse morbid scenarios and therefore correlate with poor prognosis.[145]

Even though the physiological nexus between RDW and cardiovascular outcomes is not completely understood, some authors propose that oxidative stress and chronic subclinical inflammation resulting in dysregulation of iron homeostasis could be the cause.[146, 147]

High baseline RDW has been considered an independent predictor of worse HF prognosis, namely HF hospitalization and all-cause mortality, after analysis of data from the CHARM Program and the Duke Databank for Cardiovascular Diseases.[145]

A 2018 investigation also recognize RDW as a long-term predictor of major adverse cardiac events.[148]

Our study seems to support these trials, since RDW correlated with all the proposed outcomes.

Additionally, in the subset of patients with HFpEF early readmission hazard was inferior to that of the general population as predictable.

We emphasize that mortality risk decreased during follow-up (HR=1.826 for early mortality versus HR=1.294 for long-term mortality) which supports our hypothesis that the first 90 days post-discharge implicate a maximum risk period that declines with time.

Likewise the other risk predictors described, the HFrEF subgroup evolved with worse long-term survival than general populations'.

9.2.3.9. Erythropoietin

Erythropoietin is a hormone produced in the juxtaglomerular cells of the kidney in response to local hypoxia (secondary to renal hypoperfusion) and/or systemic hypoxia (caused by HF, anemia, pulmonary disorders, infectious diseases), that promotes erythropoiesis.

Red blood cell production ensures oxygen delivery to the tissues.[149]

Therefore, EPO is a marker of hypoperfusion (which is a paramount characteristic of the HF syndrome), hypoxia and inflammation, and translates disease severity.[150]

Beside the hypoperfusion, hypoxia and inflammation scenario, bone marrow resistance to EPO due to iron and other hematopoietic factors paucity, often seen in HF patients, could also play a role in EPO's increased production.[151]

The complexity of these mechanisms determine a weak correlation between EPO and hemoglobin values in CHF patients, in contrast with other sets of patients.[152]

Consequently, although this hematopoietic growth factor is upregulated in anemic conditions, in CHF patients this relation is not linear.

Such finding may justify the benefit of correcting hematopoietic factors deficit (namely iron deficiency) in non-anemic patients.

High baseline levels of EPO have been described in HF patients by some authors.[152, 153]

Importantly, the relation between HF and heightened EPO values seem to correlate with hospitalization and mortality risk.

Belonje and colleges verified that higher EPO levels were independently linked to HF hospitalization and increased mortality risk at 18 months, a follow-up period similar to ours.[153]

A small-scale study of 74 patients with CHF also identified a link between elevated EPO and long-term survival.[152]

In our research erythropoietin was a prognosticator of long-term mortality, in accordance to the mentioned trials.

A linkage between EPO and short-term mortality was also encountered.

Mortality risk diminished along with follow-up, again, supporting our theory that mortality risk peaks at the first 3 months after hospital discharge and declines with time.

For the same increments of EPO, the HFrEF subgroup showed a greater long-term mortality risk than general population study, in line with the other prognosticators that we studied.

A trend-towards short-term readmission and elevated EPO values was recognized in both general population study and in HFrEF patients.

To our knowledge data addressing EPO and HF short-term outcome is scant, thus our study adds some information to this matter.

9.2.4. BIOMARKERS

9.2.4.1. Brain Natriuretic Peptides

Several biomarkers have been used in HF clinical practice, nevertheless only the brain natriuretic peptides are preconized by the current ESC guidelines for the diagnosis of HF.[1]

Although the role of natriuretic peptides as risk stratification markers and its prognostic cardiovascular value, specially estimating mortality burden, is gaining importance, the ESC considers that, still, the amount of evidence is not sufficient to recommend its use as HF prognosticators.[1]

Considering natriuretic peptide-guided therapy, the controversy of scientific evidence, also, prevent its recommendation by the ESC.[1]

On the contrary, in 2013, the American guidelines, already, stated that beside its well validated diagnostic indication, B-type natriuretic peptide (BNP) and NT-proBNP can also be applied for prognostication and to assess and adjust HF treatment, given that the decline of its serum values correlates with a more favorable cardiovascular outcome.[41]

Beside its diagnostic utility, some authors claim that natriuretic peptides determination is equally suitable to estimate prognosis in both acute decompensated HF and CHF.[154]

Brain natriuretic peptide is a hormone first isolated in the brain, nevertheless it is produced by the heart, namely the myocytes of the ventricles.

It is the active product of the cleavage of the prohormone proBNP that, also, generates NT-proBNP which is biologically inactive.

The BNP gene is activated in response to ventricular pressure overload,[155] which produces the prohormone in order to inhibit the renin-angiotensin-aldosterone system, systemic and renal sympathetic activity and endothelin-1.[156]

These effects promote natriuresis, diuresis and vasodilation.

Natriuretic peptides, bradykinin and adrenomedullin are vasoactive endogenous peptides that are subtract to neprilysin, an enzyme produced in the proximal tubules of nephrons.[157]

The possibility of preventing cardiac hypertrophy and fibrosis, beside the beneficial natriuretic, diuretic and vasodilator effect, through neprilysin blockage has been proposed.[158]

For a long time, it has been postulated that endothelin-1, transforming growth factor-β and angiotensin II act as local mediators in cardiac fibrosis.[159]

Tamura N et al., investigated the potential antifibrotic role of BNP, by recognizing that BNP knockout mice developed enhanced cardiac fibrosis.[160]

A recent multicenter study, by Miao ZL et al., that encompassed 421 patients with acute myocardial infarction submitted to primary percutaneous coronary intervention recognized an improvement in the

laboratory panel, cardiac function parameters and cardiovascular outcome in the subset of participants that received early intravenous recombinant human brain natriuretic peptide.[161]

The investigators confirmed that the recombinant human brain natriuretic peptide arm showed a significant decrease in serum concentrations of Cardiac Troponin T (cTnT) and NT-proBNP, developed an improved left ventricular end-diastolic diameter, stroke volume and LVEF, and ultimately cardiac death.[161]

In the opinion of some clinical investigators, natriuretic peptides plasma concentration correlates with the severity of systolic dysfunction.[162, 163, 164]

We validated this assumption since NT-proBNP values were inversely proportional to LVEF.

Researchers from the Framingham Heart Study inferred that most of the variability in NT-proBNP in groups of individuals is owed to among-person variability, rather than within-person variability. [165]

Raymond I et al., had studied the variables on the plasma level of natriuretic peptides, a couple of years before, and reached the same conclusions.[166]

Renal impairment increases BNP and NT-proBNP levels because renal clearance represents an important mean of their elimination, therefore the correlation between GFR and plasma ranges needs standardization.[167]

In our investigation NT-proBNP values were inversely proportional to baseline and admission GFR.

Regarding the interpretation of natriuretic peptides, in accordance to data from the Framingham Heart Study one must consider that its serum concentration tends to augment with age and in women.[165]

In our study no robust correlation was acknowledged regarding gender.

As for age relation, as referred previously, population homogeneity forbad such inferences.

In our research the plasma concentration of brain natriuretic peptide was lower in the obese, reproducing what was described by Das and colleges.[168]

Apart from the above statements, an interpersonal discrepancy has been denoted as not all HF symptomatic patients have increased natriuretic peptides measurements and, on the other hand, not all asymptomatic subjects have low serum concentrations.[169, 170]

The American Task Force underlines that although low levels of brain natriuretic peptides have a negative predictive value to rule out HF of 96% for BNP and 99% for NT-proBNP and that increased levels have a positive predictive value to diagnose HF of 79% and 76%, respectively, one must have in mind that these biomarkers are secreted due do ventricular stress and that other etiologies of cardiac injurie beside HF (like acute coronary syndromes, atrial fibrillation, myocarditis) and even non-cardiac conditions (namely advanced age, renal impairment, anemia and pneumonia) may also determine high levels of these peptides.[41]

Therefore, the association with other biomarkers and prognosticators is desired to enhance natriuretic peptides' diagnostic and prognostic efficacy.

The association of NT-proBNP to other biomarkers (namely hsTnT, Gal-3 and sST2) added prognostic information that will be discussed in the respective sections.

In our research NT-proBNP was a powerful prognosticator of short and long-term mortality.

Admission NT-proBNP was a predictor of 90 day post-discharge all-cause mortality, as referred by Waldo and collaborators.[171]

We established that admission NT-proBNP was a predictor of long-term overall mortality, as described by a substudy of the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial, also, comprising patients with symptoms of HF at rest or on minimal exertion.[172]

In parallel with a prospective trial addressing ADHF patients, during one-year follow-up, with a year mortality close to ours (35%),[173] we verified that discharge NT-proBNP levels correlated with long-term mortality.

Notably, the mortality hazard associated to elevated admission NT-proBNP was greater in the early post-discharge period weaning along with follow-up.

We highlight that elevated discharge values of NT-proBNP posed a greater long-term mortality risk than admission concentrations, which supports the utility of serial determinations and that, probably, aiming a lowest NT-proBNP as possible during hospitalization could be advantageous.

Logeart et al., performed serial BNP measurements in patients hospitalized for decompensated CHF and recognized that patients that maintained high BNP levels, despite adequate treatment evolved with a worse prognosis.[174]

Waldo SW et al. sustained this hypothesis, as discharge values of NT-proBNP showed the greatest prognostic yield for all-cause mortality.[171]

Savarese conducted a meta-analysis of 2686 CHF patients that tested natriuretic peptide-guided therapy against standard clinically-guided therapy, and found an improvement in mortality and hospitalization rate in the peptide-guided therapy group.[175]

Also relevant, was the fact that a meta-analysis proved that serial analysis was useful to optimize HF therapy, particularly in the absence of clinical exacerbation.[176]

All these findings corroborate the conjecture that the use of serial natriuretic peptide assays, as performed in our study, can add significant information to single measurements.

We believe that, our findings fundament the utility of NT-proBNP as a predictor of CV outcome beyond its well validated diagnostic purpose.

9.2.4.2. Troponins

Troponin is a complex of three globular contractile regulatory proteins (troponin T, I and C) situated in the thin filament of striated muscle that inhibits contraction through the blockade of the interaction of actin and myosin.[177]

Cardiac troponin I and T exist exclusively in the cardiac muscle, enabling these myofibrillar proteins to be specific and sensitive of myocardial injury.[178]

Conversely, type C troponin is found concomitantly in the skeletal muscle, preventing it from being a specific cardiac biomarker.[178]

Scientific development granted an improvement in troponin assays through highly sensitive troponin T.[178]

This biomarker warrants a finer detection of cardiac injury than the standard assays, which permits to identify minimum cardiac damage.

Elevated troponin is indicative of cardiomyocyte injury due to any cause, resulting from myocardial stress and myocyte death.[179]

Ischemia is a major cause of myocyte lesion, nevertheless, inflammation, oxidative stress and neurohormonal activation also promote cardiac damage.[179]

Meijers et al., acknowledged that hsTnT has a low biological variation, meaning that even slight variations are accurate to identify a real change.[42]

This feature may render hsTnT appropriate for follow-up and biomarker tailored strategy.[42]

Discrete elevations of troponins are present in HF patients without ischemia, and correlate with death hazard, like denoted by Horwich et al.[180]

A prospective study of 107 patients hospitalized with ADHF with similar characteristics to our population study (mean age 72 ± 13 years, 44% male and LVEF 47 ± 15%) recognized that hsTnT was an independent prognosticator of long-term survival.[181]

Alike the cited trial, we established a consistent relation between hsTnT and long-term mortality risk (P-value=0.023).

We emphasize that the long-term mortality risk augmented up to 5 times for a cut-off of hsTnT ≥52 ng/L.

Pascual-Figal et al., acknowledged that when used together, hsTnT and NT-proBNP provided complementary prognostic data and superior risk stratification.[181]

We were able to confirm these observations as hsTnT and NT-proBNP evaluated independently did not correlate with early readmission, but when assessed together a link was identified.

Additionally, the combined evaluation of the myonecrosis marker and of the myocardial stretch peptide further increased the long-term mortality risk identified with the evaluation of each biomarker.

Of interest, the highly sensitive assay identifies a wider range of individuals, including seemingly healthy subjects.[182]

This fact raises the possibility of diagnosing subclinical disease, allowing a precocious intervention able to change the disease's course and therefore a more effective primary prevention of CV diseases.

In the Val-HeFT trial, cTnT was detectable in only 10.4% of the population study while hsTnT was perceived in 92% of the population. The elevation of hsTnT was significantly associated with mortality in the 90% of the population with undetectable cTnT.[183]

Such results suggest that hsTnT is a more sensitive predictor of HF survival than cTnT, enabling the detection of at-risk patients otherwise neglected by traditional assays.

Our research supports the idea that hsTnT stands as a more accurate CV outcome predictor as no correlations between cTnI and study outcomes were identified.

The exposed evidence suggests that troponins are more than an acute cardiac injury marker, playing an interesting role in the prognostication and risk stratification of cardiac disease and allowing the detection of early stage HF.

Braunwald foresaw, a decade ago, that as the sensibility of troponins perfect, this biomarker would be routinely used, in addition to natriuretic peptides, to define prognosis and to monitor response to HF treatment. [179]

The American HF guidelines recommend cardiac troponin measurement to delineate prognosis of ADHF.[52]

9.2.4.3. Galectin-3

Galectin-3 is a soluble β-galactoside-binding protein which is produced by activated macrophages. It plays a pivotal role in cardiac fibroblast proliferation and collagen synthesis which result in LV stiffness and ultimately in ventricular dysfunction.[184, 185]

Similarly, physiologic myocardium ageing is marked by apoptosis, resulting in decreased cardiomyocyte number, collagen deposition and increased cardiomyocyte size. Such cellular changes, seen in the senescent heart, promote cardiac fibrotic remodeling and evolve to ventricular diastolic dysfunction.[186]

Fibrosis, the histologic reparation process in which *restitutio ad integrum* of the injured tissue cannot be achieved, being replaced by fibroblasts, seems to be the underlying mechanism of the Gal-3 inflammation pathway.

Although this acute and chronic inflammation marker is not specific of cardiac injury, since it has been involved in various organs fibrotic degeneration processes[187] and even with ageing[188] and tumor mediation[189] there is growing scientific evidence that consistently support its cardiovascular prognostic value.

The rationale for the utility of Gal-3 in HF clinical practice is based in the fact that the healthy heart expresses minimum amounts of Gal-3, which increases as HF progresses[190, 191] and that, albeit, not being specific of myocardium injury, several trials have consistently acknowledged its prognostic value evaluated separately or in combination with natriuretic peptides.

Shah et al., stressed that Gal-3 plasma levels could be elevated, even, in the subclinical phase of HF, which could be useful in the assessment of the progression to symptomatic HF and allow a precocious intervention in HF management.[192]

Women[193, 194] and older patients [192, 193, 194, 195, 196] have higher levels of Gal-3, and one particular study found that individuals above 80 years old not suffering from HF frequently have Gal-3 levels superior to 20 ng/mL. Such conclusions raise the question of establishing cut-offs according to age groups like other biomarkers, namely natriuretic peptides.[194]

Patients with greater comorbidity burden, namely obesity, dyslipidemia, arterial hypertension, atrial fibrillation[194, 195] and renal impairment[192, 193, 194, 196] also presented with higher Gal-3 levels.

We were able to identify an inversely proportional correlation between Gal-3 levels and GFR for both baseline and admission values.

A trend towards elevated Gal-3 values and ischemic heart disease was also observed.

In our research no correlation was identified between Gal-3 serum determinations and gender or LVEF, findings reminiscent of those of a sub analysis of the Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) study.[197]

Concerning to NYHA functional class no correlation with Gal-3 was identified by us, likewise the sub analysis of the Deventer-Alkmaar heart failure (DEAL-HF) and ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE HF) trials.[192, 193, 198, 199]

We are able to verify the assumption of numerous authors that patients with higher serum levels of Gal-3 have, also, higher levels of brain natriuretic peptides.[192, 193, 194, 195, 196]

Albeit these known interindividual variations, Schindler et al., confirmed that Gal-3 could be a useful tool in assessing HF patients due to its low biological variation indices.[200]

Meijers WC et al. observed an association between elevated plasma galectin-3 and near-term readmission in HF, as patients with Gal-3 levels greater than 17.8 ng/mL presented twice to three times the risk of rehospitalization at 30, 60 and 90 days post discharge, when compared to those who had Gal-3 levels inferior to 17.8 ng/mL.[201]

We confirmed that Gal-3 levels correlated with short-term rehospitalization and that the risk increased throughout terciles.

Moreover, the addition of high values of NT-proBNP to Gal-3 further increased the risk of short-term rehospitalization.

In syntony with the addressed prognosticators, the previous multimarker strategy represented a greater risk for short-term rehospitalization in the HFrEF group.

Importantly, galectin-3 was an independent predictor of short-term mortality in our study and, again, the combination with NT-proBNP implicated a greater risk than each taken solely.

The PRIDE sub analysis demonstrated that the subjects who deceased in the first 60 days after hospital discharge showed Gal-3 plasma levels superior to those that survived.[198]

The referred study found that Gal-3 was an accurate predictor of mortality and of the binomium mortality/recurrent HF.

The investigators, also, established that the conjoined use of Gal-3 and NT-proBNP was more sensible to prognosticate mortality hazard than each biomarker analyzed separately.[198]

We acknowledged that Gal-3 was, also, an independent predictor of long-term mortality and that multimarker strategy with NT-proBNP perfected risk stratification, as seen in the other proposed endpoints.

Data from the DEAL-HF study showed that Gal-3 was a reliable mortality predictor in NYHA functional class III and IV patients, since a proportional increase in all-cause mortality was noted throughout the Gal-3 quartiles.[193]

The sub analysis of the Coordinating Study Evaluating Outcomes of Advising and Counseling Failure (COACH) trial noticed that the prognostic efficacy of the combination of Gal-3 and BNP (AUC 0.69) was superior to Gal-3 alone (AUC 0.67), which was greater than BNP's evaluated individually (AUC 0.65).[195]

Galectin-3 proved to be an interesting biomarker in our research as it prognosticated all the aimed outcomes.

Remarkably we achieved statistical significance using a cut-off lower than the generally preconized, nevertheless the serum values of Gal-3 vary with the quantification method, which prevents direct comparison with studies that used a different lab kit.

The current data supports that although Gal-3 has a diagnostic value inferior to the traditional natriuretic peptides, when assessed separately its prognostic role looks to be superior, achieving an even greater accuracy when both biomarkers are analyzed together.

The weight of evidence suggests that Gal-3 is a useful tool to detect and stratify high risk HF patients, enabling to plan their follow-up, in order to reduce the notorious high rates of near-term rehospitalization and mortality.

The sum of relevant evidence led the 2013 American guidelines to recommend the measurement of Gal-3 for additive risk stratification in patients with acute or ambulatory HF.[41]

Even though the Gal-3 extracellular releasing mechanism needs clarification, there is substantial evidence linking this inflammation surrogate marker to cardiac remodeling and ultimately to HF inexorable continuum.

Given this, one must question if in a near future Gal-3 suppressors or inhibitors of its pathways will ascend as new cardiovascular therapeutic targets.

9.2.4.4. Pro-ADM

The role of mid-regional pro-adrenomedullin in the management of HF urges clarification, yet the available data support its application as a trustworthy biomarker of short and long-term prognosis in both decompensated and stable chronic HF.

Nevertheless, the scientific evidence favors short-term assessment.

Concerning diagnosis its accuracy seems to be doubtful.

Adrenomedullin is a 52-amino acid peptide discovered in pheochromocytoma cells in the adrenal medulla.

It is a ubiquitous peptide and apart from the heart it is also produced by several other tissues namely endothelial cells, vascular smooth muscle cells, fibroblasts, adipocytes.[202, 203]

The main organs (central nervous system, kidneys, lungs, gastrointestinal organs) also secret ADM.

Considering the myocardium, ADM expression is stimulated by pressure or volume overload and ventricular wall stretching, counteracting with a reduction in preload and afterload by promoting diuresis, natriuresis and vasodilation.[202, 203]

An additional cardioprotective benefit has also been hypothesized, as it has been related to a reduction in cardiac hypertrophy, ventricular remodeling and fibrosis.[202, 203]

Thus ADM's role in HF's pathophysiology is based in the fact that it is a cardiomyocyte strain marker with vasoactive properties.

The cleavage of pro-hormone pro-ADM originates ADM and MR-proADM.[202, 203]

Direct quantification of ADM is not feasible due to its in vitro instability, short half-life and the existence of binding proteins. However MR-proADM besides being stable, allowing dosing, correlates with ADM levels.[202, 203, 204]

Likewise other HF markers MR-proADM is elevated in other cardiovascular pathologies (myocardial infarction, systemic and pulmonary hypertension) and even in non-cardiologic conditions (kidney failure and sepsis).[202, 203]

Data from the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca-HF (GISSI-HF) trial, which comprised 1237 patients with chronic and stable HF, suggested that as with natriuretic peptides, one must bear in mind that MR-proADM serum concentration augments with ageing, systolic dysfunction and renal impairment. Similarly, the female gender has heightened levels and individuals with higher body mass index show decreased MR-proADM values.[205]

Furthermore, MR-proADM interpretation is compromised by the absence of a well-established threshold.

In our research a trend towards MR-proADM values and NYHA functional class IV was observed.

Von Haehling et al., addressed 501 CHF patients, and verified, too, that MR-proADM plasmatic levels increased with NYHA class.[206]

We point out that in HFmrEF patients a trend towards MR-proADM and early readmission was identified, since that, to our knowledge data addressing this topic is limited.

We relied on several trials to pursue relevant data regarding this new biomarker, nevertheless our results were somehow frustrating as no statistically significant result was achieved, possibly due the reduced member of participants in our study.

9.2.4.5. ST2

Suppression of tumorigenicity 2 is a promising biomarker that seems to correlate more accurately with cardiovascular remodeling and fibrosis than MR-proADM, beside its precision in estimating the outcome of HF, improving natriuretic peptides' performance.

There is consistent evidence that suggests that its biologic variability is considerably lower than that of the natriuretic peptides, which could warrant a greater prognostic sensibility.

Head-to-head comparison of ST2 and Gal-3 in CHF risk stratification seems to favor ST2 over Gal-3.[207]

Concerning diagnosis, as with MR-proADM, its value appears to lack significance.

The 2013 American guidelines recommend the measurement of ST2 for additive risk stratification in patients with acute or ambulatory heart failure.[41]

Suppression of tumorigenicity 2 belongs to the IL-1 receptor family. There are two main isoforms, a transmembrane receptor (ST2L) and a soluble receptor (sST2) which is the circulating isoform that can be detected in serum.[208, 209]

The pathophysiological role of this biomarker in HF, is based in the cardioprotective effect of the interaction of ST2L and its ligand, IL-33, a cytokine released in response to cellular damage, including cardiomyocyte strain.[208, 209]

This pathway regulates the myocardial reaction to biomechanical overload in strained cardiac fibroblasts and cardiomyocytes, resembling natriuretic peptides function.[210]

The duality IL-33/ST2L, participates in several inflammatory conditions, beyond cardiac distress, by triggering Th2 effector cells which secretes cytokines.[208]

It has been postulated that the IL-33/ST2 pathway, although unspecific, is expressed in cardiac fibroblasts and cardiomyocytes due to myocardial damage.[208, 209]

Its beneficial cardiac effect derives from the counterbalance of cardiac apoptosis, myocardial fibrosis, cardiomyocyte hypertrophy, and ultimately, by increasing myocardial function.[208, 209]

This advantageous effect is abrogated by the soluble isoform, which acts as a decoy receptor, by binding to IL-33 and blocking its signaling.[208, 209, 211]

Thus, the rationale of using sST2 as HF biomarker relies on the fact that its levels are increased in cardiomyocyte damage, namely remodeling, fibrosis and hypertrophy.[208, 209]

It has been stated that sST2 evaluation could play a role in the assessment of ventricular remodeling since elevated serum concentrations reliably correlate with reduced ejection fraction, left ventricular enlargement and hypokinesia.[212]

In addition, a link between this marker and left ventricular end-diastolic volume was recognized, raising the possibility of monitoring structural cardiac modifications.[213]

Similarly to the other discussed biomarkers sST2 is not specific to HF, and rises in other cardiovascular conditions like ischemic and valvular heart disease and arterial hypertension.[211]

Given this, sST2 lacks disease specificity and, consequently, is a poor marker for the diagnosis of HF.[211]

Nevertheless, like galectin-3 and MR-proADM, it seems to be useful in stratifying both acute and chronic HF severity and determining the prognosis.[211]

This novel biomarker emerges as an independent predictor of mortality, in both acute and chronic HF, irrespective of the etiology of HF or LVEF, and as a complement to other markers.[214]

Likewise the natriuretic peptides and MR-proADM, sST2 levels vary inversely with the GFR, but its prognostic accuracy does not seem to be compromised by renal function.[215, 216, 217]

We verified that sST2 levels correlated inversely with baseline and admission GFR (P-value<0.001 for both).

Nonetheless, according to Rehman S et al., these associations were weaker than those related to natriuretic peptides', raising the hypothesis that sST2 prognostication sensitivity is not significantly influenced by comorbidities.[215]

Piper S et al., also documented that the biologic variability of sST2 is substantially inferior to that of natriuretic peptides, thus more precise, alluding that this molecule could represent a breakthrough in CHF assessement.[218]

As for age, like defended by Rehman S et al.,[215] no consistent correlation was identified in our investigation.

Some authors suggest that greater sST2 values are present in the male gender.[213, 217]

In our investigation a trend towards sST2 levels and male patients was also identified.

The Metabolic Efficiency With Ranolazine for Less Ischemia in the Non-ST-Elevation Acute Coronary Syndrome Thrombolysis in Myocardial Infarction 36 (MERLIN-TIMI 36) trial stressed the eventual necessity of defining gender-based thresholds.[219]

Similarly to NT-proBNP, obese patients had lower amounts of sST2 in our study. To our knowledge data establishing a statistical significant relation between sST2 and obesity is scant.

Such finding could be interpreted as since sST2 elevation is a marker of worse outcome, and in our study the obese evolved with a better long-term survival, it is reasonable that these two variables vary inversely.

Furthermore, sST2 elevation was, also, a predictor of long-term mortality.

Although the prognostic cutoff of 35 ng/mL is widely accepted,[213, 217, 219] there is still some argument surrounding the ideal sST2 upper reference limit for cardiovascular risk stratification.

Our investigation adds controversy to this discussion as we were able to establish a lower threshold of 24.78 pg/mL, with a significant 5 times increased hazard for long-term mortality.

Additionally, for each increment of, as little as, 10 pg/mL of sST2 the risk for long-term mortality elevated up to 37.2%.

However the different methods of quantifying sST2 are not directly comparable and it is essential to know which method was used when interpreting the results.[220]

A cohort of 346 patients with ADHF, by Rehman et al., corroborated the relation between heightened levels of sST2 and poor long-term outcome (the AUC ROC for death at 1 year was 0.71).[215]

Our finding is, also, sustained by the PRIDE trial, since a trend towards high concentrations of this biomarker and one year-mortality was acknowledged.[221]

Relevantly, the mutual quantification of sST2 and NT-proBNP improved risk stratification.[221]

The association of NT-proBNP to sST2 determination was also useful in our study as it further increased the long-term mortality risk.

Subgroup analysis showed that, for HFpEF patients, the addition of serum values of admission NT-proBNP ≥1800 ng/L to sST2 ≥24.78 pg/mL further increased the hazard of long-term mortality compared to the individual evaluation of sST2 (HR=5.2 Vs HR= HR=8.381, respectively).

Rehman and colleges were, also, able to recognize that both sST2 and NT-proBNP were powerful prognosticators of long-term mortality.[215]

Notably, the patients with simultaneous elevation of sST2 and natriuretic peptide had a higher mortality burden.[215]

Remarkably the addition of Gal-3 values ≥9.99 ng/mL to sST2 assessment implicated a 6 times augmented long-term mortality hazard, which was comparable to the conjoined evaluation of sST2 and admission NT-proBNP ≥21336 ng/L.

We underscore that, resembling other multimarker strategies discussed in this research, long-term mortality risk linked to sST2 and Gal-3 simultaneous quantification, was greatest in the HFrEF and lowest in the HFpEF. General population study showed an intermediate risk.

We could not achieve a link between sST2, nor with Gal-3 ≥9.9 ng/mL, and early mortality when each biomarker was assessed isolatedly, however with their combination statistical significance was met.

The combination of sST2 ≥24.78 pg/mL and Gal-3 ≥9.99 ng/mL implicated an interesting 8 times increased hazard for early mortality.

Subgroup analysis showed that in the HFpEF subset of patients, joining determinations of sST2 ≥24.78 pg/mL and Gal-3 ≥10.97 ng/mL resulted in an impressive HR of 19.3.

Although there are several studies relating sST2[215, 53] and Gal-3 to short-term mortality separately[198] to our understanding studies focusing on a multimarker approach regarding this outcome lack.

Therefore our research brings new information to this topic.

10. STUDY LIMITATIONS

Although the authors followed the patients thoroughly, the rehospitalization rate may not be 100% accurate as some patients could be readmitted into a different hospital. However, we believe that such cases were trivial since that the area code hospital of the population was the Hospital de Santa Maria.

The present trial is hindered by the fact that the population was relatively small, making some appraisals problematic without accurate statistical power.

To analyse the prognostic precision of each biomarker and to implement a multibiomarker strategy, specific cut-offs were defined, however some thresholds are not standardized and different methods of quantifying some biomarkers are not directly comparable which has to be taken into account when comparing to other studies.

11. STRATEGIES TO DECREASE READMISSIONS AND MORTALITY

In a study, conducted by Sousa-Pinto, all hospitalizations in public hospitals in Portugal mainland from 2000 to 2008 were analyzed, aiming to describe non-planned hospital readmissions occurring in a period of 30 days post-discharge.[28]

The aforementioned research apart from studying the rate evolution of readmissions in that period, focused, specifically, on readmissions related to ADHF.

Special attention was paid to HF due to its high socio-economic impact[222] related to the high risk of readmission and because scientific evidence demonstrated that the implementation of strategies directed to patients with this illness decreases the readmission episodes[223, 224].

At the time this report was a breakthrough as there were no similar studies in Portugal.[28]

From the 5 514 331 non-elective hospitalizations occurring in the studied period, 4.1% corresponded to readmissions.

The nosological entities were grouped in large diagnostic categories; a larger readmission rate was verified in the group of "Myeloproliferative Diseases & Disorders, Poorly Differentiated Neoplasms".

This heterogeneous nosological group encompasses hematological neoplasms, occult malignant cancers and cancer metastasis, which due to its clinical severity and inherent side effects related to the targeted therapy (namely chemotherapy, radiotherapy and immunosuppressants) a high number of readmissions is expected.[28]

Minding this fact, we excluded patients with active neoplasm so that it would not bias the readmission rate in our investigation.

In the specific case of HF (n = 315 321) the rehospitalization rate was of 6.7%, below the rates reported in similar studies. The authors justified this lower than expected readmission rate with fact that the patients' identification code kept changing from year to year in the same hospital and some patients were readmitted into a different hospital.[28]

During the period 2000 to 2008, the rate of readmissions due to HF increased significantly. In relation to in-hospital mortality there was also an increase in the given period, both in the readmitted and non-readmitted group, with no significant difference between groups (17.2% *vs.* 16.9% respectively), although a greater increment was found in the readmitted group.[28]

The authors argued that the data provided by their study could be used by the Portuguese National Health System to improve hospital organization and therefore reduce the readmission burden.

Several healthcare programs have been applied to monitor HF outcome, nevertheless most were small and underpowered, the targeted populations were not homogeneous and the strategies varied widely among studies which prevents us from inferring its real impact.

Unfortunately, one must agree that evidence addressing multidisciplinary approach to the HF population is still scarce and lacks statistical power.

A close follow-up is essential to identify and treat slight acute decompensations, preventing progressive deterioration and consequent hospitalization.

A document elaborated by the National Heart Foundation of Australia defined a set of principles addressing care delivery, to enhance health professionals' practice, aiming at improving CHF patients' quality of life and avoid hospitalizations.[225]

The Australian Task Force carried out a systematic review of randomized trials evaluating multidisciplinary strategies for the management of HF patients at high risk for admission, and concluded that in-person specialized follow-up at home or in a healthcare facility reduced HF hospitalizations, all-cause hospitalizations and mortality.[225]

Patients that were contacted by telephone on a regular basis by their physician had less HF hospitalizations, although no difference in all-cause hospitalizations or mortality was found.[225]

A meta-analysis by Foody et al. validated the positive impact of structured telephone support in HF readmission, plus HF mortality.[226]

Regarding telemonitoring programs, in which data (symptoms, physiologic parameters) is remotely transmitted to the healthcare providers, without visits by the health personnel or direct phone calls, there is some controversy as some meta-analysis mentioned a trend towards reduction in HF hospitalizations and mortality,[227] while others found no benefit in the outcome[226, 228].

Patient awareness is fundamental to promote self-care.

The Australian Task Force also verified a decrease in HF hospitalizations and all-cause hospitalizations in healthcare programs focused on self-care, but no significant impact on mortality was identified.[225]

An observational study of almost 11 000 patients sustained that patients revaluated within the first 30 days post-discharge by both a primary care physician and a cardiologist had a significant lower one year-mortality compared to those observed solely by a primary care clinician. For the given period of time patients evaluated only by a generalist had a lower mortality rate than patients with no post-discharge assistance at all.

The results were explained by the fact that patients cared by both a specialist and a generalist had LV function assessment more often and were more likely to be treated with evidence-based drugs.[229]

Nowadays there has been a consistent proliferation of multidisciplinary HF clinics (the so called "infusion centers") that administer intravenous drugs, either diuretics or ionotropics, to outpatients.

A meta-analysis including forty-seven trials addressing healthcare programs enrolling predominantly patients with moderate to severe HF with a mean age of 70 years, confirmed a clear benefit in three- to six-month readmission and mortality rates when such patients were treated in these clinics.[230]

An observational study demonstrated that hospitals with the lowest early post-discharge reexamination rate (within the first week) had a 3% higher 30-day re-hospitalization incidence compared to those that were prone to early post-discharge appointment.[231]

The Portuguese Consensus Statement for the improvement of HF, preconized a multidisciplinary management of HF patients,[21] since specialized HF multitask teams have proved to be cost-effective and to improve patients' outcome by reducing admissions and mortality[1].

Beside health care professionals recommendations, the Statement also focuses on patient and care giver education.[21]

The Portuguese Task Force [21] also suggested, in syntony with the latest European HF guidelines[1], an early post-discharge reevaluation, ideally after one week by a primary care physician and, at most, after two weeks by a specialist.

The Statement also stresses the crucial importance of HF Day-Hospitals and cardiac rehabilitation programs in todays´ long-term patients' approach, earning a class IA from the actual guidelines[1], emphasizing the necessity of creating more specialized ambulatory centers in Portugal.[21]

Portugal is one of the 45 countries, that integrates the Optimize Heart Failure Care Program (www.optimize-hf.com), implemented worldwide, since 2013.[232]

This Program aims at improving outcomes following HF hospitalization through inexpensive initiatives to optimize prescription of evidence-proved drugs, patient and care givers instruction and involvement, and post-discharge planning.

The Program provides best practice clinical protocols based on the latest ESC guidelines[1], pre- and post-discharge checklists, and 'My HF Passport', a printed and smart phone application to improve patient knowledge of CHF and promote involvement in care adherence.

The 'My HF Passport' also allows the patient to register relevant signs and symptoms, granting the physician the opportunity to optimize the treatment.

Its purpose is to guarantee that the in-hospital measures are continued post-discharge, particularly in the most vulnerable period of the first months.[232]

'Get With the Guidelines-Heart Failure' (GWTG-HF) is an in-hospital program, sponsored by the AHA, for improving care through promoting adherence to guidelines.

This registry is the continuation of the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) program[233] that resembles the European program.

There is evidence that the Program implementation resulted in 30-day readmission for HF reduction,[234] still an USA national survey evidenced that the adherence can be furthermore improved[235].

As advocated the first 30 to 90 days post-discharge is a critical period for HF patients and should be an opportunity to intervene and try to change the syndrome's course.

Since it is not viable to reevaluate all the HF hospitalized patients in this strict period of time, it is mandatory to identify and target high risk patients for early readmission and mortality and be assertive in this “golden period”.

12. CONCLUSIONS

According to our study, the risk factors for early readmission were: the accumulated length of stay, multiple hospitalizations, renal failure, cardiorenal syndrome, RBBB, anemia, elevated RDW and Gal-3 values.

We acknowledged the following risk factors for early mortality: the absence of inferior vena cava inspiratory collapse, increased LV end-diastolic volume, hepatomegaly, low systolic and diastolic blood pressure, renal failure, cardiorenal syndrome, LBBB, absolute iron deficiency, elevated RDW, EPO, NT-proBNP and Gal-3 determinations.

The combination of biomarkers added relevant data, namely the addition of sST2 to Gal-3 which further increased the risk for early mortality.

Small sample size forbad significant statistical correlation between the defined outcomes and the etiology of HF, the NYHA functional class, therapeutics and the biomarker Pro-ADM.

We believe that this trial could contribute to risk-stratify heart failure patients, as several variables were addressed from symptoms, to electrocardiography, echocardiography, routine lab tests and ultimately new era biomarkers.

Our results may raise, simultaneously, the interest in some neglected quotidian parameters and in novel biomarkers.

National data regarding this matter is scant, so this study may help to better understand our heart failure population.

The conclusions provide real world data, as it was collected from a subset of patients randomly hospitalized for acute decompensated chronic heart failure in an Internal Medicine ward, and similar findings were reported in larger and multicenter investigations, which corroborate and in a certain way validate the results.

Given its complexity, strategies to reduce heart failure rehospitalization and mortality should encompass the optimization of evidence-based treatment, addressing assertively the etiology of heart failure and concomitant comorbidities, tight follow-up (a multidisciplinary approach and first and foremost the widespread of Heart Failure Day-Hospitals to stabilize patients with minor decompensations preventing the worsening of the condition and inevitably the admission to ward) and patient education.

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15. ACKNOWLEDGMENTS

À minha Família
Ao meu Orientador
À Dona Marlene Góis,

Pelo apoio incondicional.

16. ATTACHMENTS

CENTRO ACADÉMICO DE MEDICINA DE LISBOA

Exmo. Senhor
Dr. Mário Barbosa
Serviço de Medicina I D
Centro Hospitalar Lisboa Norte, E.P.E.

Lisboa, 28 de Julho de 2016

Nossa Refª. Nº 64/16

Assunto: Projecto de Investigação **"Determinantes da Readmissão Precoce na Insuficiência Cardíaca Crónica"**

Relator - *Prof. Doutor José Luis B. Ducla Soares*

Pela presente informamos que o projecto citado em epígrafe, obteve, na reunião realizada em 20 de Julho de 2016, parecer favorável da Comissão de Ética.

Mais se informa que o referido estudo foi autorizado pela Sra. Directora Clínica, Dra. Margarida Lucas.

Com os melhores cumprimentos,

O Presidente da Comissão de Ética do CAML

Prof. Doutor José Pereira Miguel

COMISSÃO DE
ÉTICA DO CENTRO ACADÉMICO DE MEDICINA DE LISBOA (CHLN/FMUL/IMM)
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CENTRO HOSPITALAR LISBOA NORTE, EPE | HOSPITAL DE SANTA MARIA | Hospital Pulido Valente

CONSENTIMENTO INFORMADO, LIVRE E ESCLARECIDO PARA PARTICIPAÇÃO EM INVESTIGAÇÃO*

Título do estudo: *DETERMINANTES DA READMISSÃO PRECOCE NA INSUFICIÊNCIA CARDÍACA CRÓNICA*

O actual projecto de Investigação insere-se num estudo que decorre no âmbito do Mestrado em Doenças Metabólicas e Comportamento Alimentar da Faculdade de Medicina da Universidade de Lisboa e tem como principal objectivo caracterizar os doentes de risco para readmissão precoce por insuficiência cardíaca (definida como reinternamento até aos 90 dias pós-alta), a fim de, perante os resultados obtidos, poderem ser consideradas estratégias que permitam reduzir as readmissões e melhorar o prognóstico.

Venho desde já agradecer a sua colaboração neste projecto de investigação, que espero aceite participar.

Para tal iremos necessitar de colher uma mostra de sangue para exames laboratoriais e consultar o seu processo arquivado no Serviço de Medinica I D.

Por este motivo a sua participação, disponibilizando a consulta anonimizada do seu processo e alta, é fundamental.

Este projecto não lhe trará nenhuma despesa ou risco. Qualquer informação será confidencial e fornecida de forma anonimizada através de um médico do serviço (equipa do Prof. Doutor Luiz Filipe Menezes Falcão) não sendo revelada a terceiros. A informação recolhida poderá eventualmente ser publicada em Revista Médica da especialidade, sem possibilidade de identificação do doente.

A sua participação neste projecto é voluntária e ser-lhe-á dada sempre a possibilidade de alterar o sentido da sua declaração de participação ou recusar participar, sem que tal tenha consequências para si.

Caso pretenda participar no projecto, assine o documento

Pode contactar-me para o seguinte número _____

Por favor não hesite contactar-me para qualquer Informação adicional que necessite.

Muito obrigado

Nome do investigador: Dr. Mário Barbosa

Assinatura: _____ **Data:** ___/___/_____

Declaro ter lido e compreendido este documento, concordo em participar no projecto de forma voluntária, anónima e confidencial

Nome:_____

Assinatura: _____ Data: ___/___/_____

*de acordo com a Declaração de Helsínquia e a Convenção de Oviedo

REGISTO DO DOENTE

NID: _____

Serviço: _____

Nome Completo: _____

Idade: ___ anos

Data de Nascimento: __/__/____

Sexo: M ☐ F ☐

Raça: Caucasiana ☐ Negra ☐ Indiana ☐ Outra ☐

Morada (com CP): _____

Telefone/Telemóvel: _____

Telefone/Telemóvel (familiar): _____ Parentesco: _____

Causa de Internamento:

Data de Internamento: __/__/____

Internamento: Cardiologia ☐ Medicina Interna ☐ Outro ☐

Peso: _____

Altura: _____

IMC[1]: _____

Superfície Corporal[2]: _____

Fórmulas

[1]IMC = Peso [kg]/Altura^2 [m]

[2] Fórmula de Dubois da Superfície Corporal (m^2) = 0,007184 X (Altura [cm])^{0,725} X (Peso [kg])^{0,425}

SINAIS E SINTOMAS DE INSUFICIÊNCIA CARDÍACA[3]

CRITÉRIOS MAJOR

Dispneia paroxística nocturna:	Sim ☐	Não ☐
Ortopneia:	Sim ☐	Não ☐
Ingurgitamento venoso jugular:	Sim ☐	Não ☐
Fervores crepitantes:	Sim ☐	Não ☐
Cardiomegália (RX tórax – ICT):	Sim ☐	ICT:_____ Não ☐
Edema pulmonar agudo:	Sim ☐	Não ☐
Galope ventricular (S3):	Sim ☐	Não ☐
Refluxo hepato-jugular:	Sim ☐	Não ☐
Dispneia em repouso:	Sim ☐	Não ☐

CRITÉRIOS MINOR

Edema maleolar:	Sim ☐	Não ☐
Tosse nocturna:	Sim ☐	Não ☐
Dispneia de esforço:	Sim ☐	Não ☐
Hepatomegália:	Sim ☐	Não ☐
Derrame pleural:	Sim ☐	Não ☐
Taquicardia sinusal (≥120bpm):	Sim ☐	Não ☐

CRITÉRIOS MAJOR OU MINOR

Perda de peso > 4,5Kg em 5 dias como resposta terapêutica: Sim ☐ Não ☐

PÂRAMETROS VITAIS

TA:

FC:

Nota

[3] ICC confirmada: se 2 critérios major ou 1 critério major + 2 critérios minor

ANTECEDENTES PESSOAIS

Cardiopatia isquémica:	Sim ☐	Não ☐	
EAM prévio:	Sim ☐	Não ☐	
Doença valvular:	Sim ☐	Não ☐	
Cardiopatia hipertensiva:	Sim ☐	Não ☐	
HTA:	Sim ☐	Não ☐	
DM2:	Sim ☐	Não ☐	
Dislipidemia:	Sim ☐	Não ☐	
Tabagismo:	Sim ☐	Não ☐	
Insuficiência renal crónica:	Sim ☐	Não ☐	
Doença vascular:	Sim ☐	Não ☐	
DPOC:	Sim ☐	Não ☐	
História familiar:	Sim ☐	Não ☐	Ignora ☐

EXAMES COMPLEMENTARES

Ureia (basal/ internamento): _____ /____

Creatininémia (basal/ internamento): _____ /____

Clearance creatinina (basal/ internamento): ____ /____

Hemoglobina: _____

VGM: _____ RDW: _____

Plaquetas: _____ Plaqueócrito:_____ VPM: _____ PDW: _____

Natrémia: _____

TSH: _____

FT4: _____

Fe sérico: _____

Ferritina sérica: _____

Saturação da transferrina: ___

CTFF: _____

Galectina-3: _____ MR-proADM:_____

ST2: _____ EPO:_____

NT-proBNP da entrada: _____

NT-proBNP da alta: _____

hsTnT: _____ TnI: _____

ECG*: RS ☐ FA ☐ BCRE ☐ BCRD ☐ HVE ☐ FLA ☐ PMD ☐

EAM ☐ localização: _____

*Surawicz B, Childers R, Deal BJ, Gettes LS. AHA/ACCF/HRS Recommendations for the Standardization and Interpretation of the ElectrocardiogramPart III: Intraventricular Conduction Disturbances A Scientific Statement From the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society Endorsed by the International Society for Computerized Electrocardiology. Journal of the American College of Cardiology. 2009;53(11):976181.

Ecocardiograma: Normal ☐

RAO	_____mm	
IRAO	_____mm/m^2	
AE MM	_____mm	
IAE MM	_____mm/m^2	
Área AE	_____cm^2	
Volume AE	_____ml	_____ml/m^2
Área AD	_____cm^2	
Volume AD	_____ml	_____ml/m^2
DTDVE	_____mm	
IDTDVE	_____mm/m^2	
DTSVE	_____mm	
IDTSVE	_____mm/m^2	
FENC	_____%	
SIV	_____mm	
PP	_____mm	
VD	_____mm	
VTDVE	_____ml	
IVTDVE	_____ml/m^2	
VTSVE	_____ml	
IVTSVE	_____ml/m^2	
FEJ	_____%	
MVE[4]	_____g	
IMVE[5]	_____g/m^2	
PSAP	_____mmHg	
VCI diâmetro	_____cm	
Vel maxE	_____m/seg	
Vel maxA	_____m/seg	
E/A	_____	
RWT[6]	_____	

Disf. Diastólica:	tipo I ☐ _____	tipo II ☐ _____	tipo III ☐ _____
Insuf. Aórtica moderada:	Sim ☐	Não ☐	
Insuf. Aórtica grave:	Sim ☐	Não ☐	
Estenose Aórtica moderada:	Sim ☐	Não ☐	
Estenose Aórtica grave:	Sim ☐	Não ☐	
Insuf. Mitral moderada:	Sim ☐	Não ☐	
Insuf. Mitral grave:	Sim ☐	Não ☐	
Estenose Mitral moderada:	Sim ☐	Não ☐	
Estenose Mitral grave:	Sim ☐	Não ☐	
Insuf. Tricúspide moderada:	Sim ☐	Não ☐	
Insuf. Tricúspide grave:	Sim ☐	Não ☐	
Prótese valvular Aórtica:	Sim ☐	Não ☐	
Prótese valvular Mitral:	Sim ☐	Não ☐	

Fórmulas

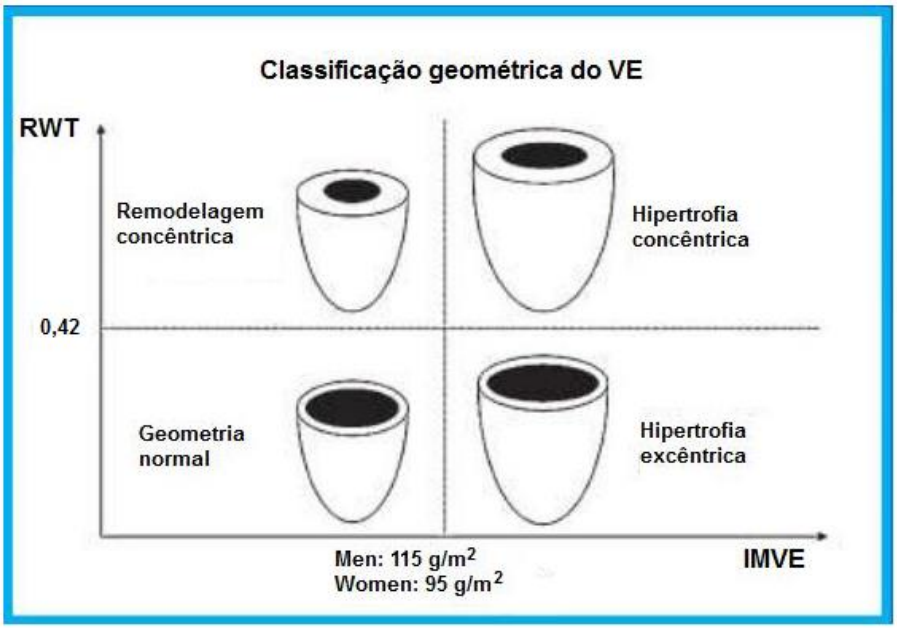
[4]MVE (Devereux modificada)(g) = 1,04 x [$(DDVE+SIVD+PPVED)^3$ - $DDVE^3$] – 13,6

[5]IMVE (g/m^2)= MVE/superfície corporal

[6]Relative Wall Thickness (RWT) ou Índice de Hipertrofia Concêntrica= (2xPP)/DTDVE

TABELA – Valores ecocardiográficos adaptados de várias tabelas, nomeadamente, LANG RM, BIERIG M, DEVEREUX RB ET AL. *RECOMMENDATIONS FOR CHAMBER QUANTIFICATION: A REPORT FROM AMERICAN SOCIETY OF ECHOCARDIOGRAPHY'S GUIDELINES AND STANDARDS COMMITTEE AND THE CHAMBER QUANTIFICATION WRTITING GROUP*, developed in conjunction with the European Association of Echocardiography, a Branch of the European Society of Cardiology. J Am Soc Echocardiog 2005;18:1440.

Valores de Referência	Mínimo	Máximo
RAO mm	22	36
IRAOmm/m^2	< 21	
AE MM mm	27	40
IAE MM mm/m^2	15	23
AE área cm^2	<20	
AE vol ml	18	58
AE vol ml/m^2	22 ±6	
AD área cm2	<20	
AD vol ml	18	58
AD vol ml/m^2	22 ±6	
DTDVE mm	39	59
IDTDVE mm/m^2	22	32
DTSVE mm	22	35
IDTSVE mm/m^2	11	21
FENC %	32	53
Esp SIV mm	6	10
Esp PP mm	6	10
VD mm	20	28
VTDVE ml	56	155
IVTDVE ml/m^2	35	75
VTSVE ml	19	58
IVTSVE ml/m^2	12	30
FEJ %	≥55%	
MVE gr	66	200
IMVE gr/m^2	44	102
PSAP mmHg	17	32
VCI diâmetro cm	≤21	
Vel maxE m/seg	0,4	1
Vel maxA m/seg	0,3	1,1
E/A	0,6	2


Classificação geométrica do VE
RWT
Remodelagem concêntrica
Hipertrofia concêntrica
0,42
Geometria normal
Hipertrofia excêntrica
Men: 115 g/m2
Women: 95 g/m2
IMVE

FÁRMACOS DO INTERNAMENTO

IECA (dose):

Sim ☐

Captopril: _____

Enalapril: _____

Lisinopril: _____

Perindopril: _____

Ramipril: _____

Trandolapril: _____

Não ☐

Interrompido ☐

ARA II (dose):

Sim ☐

Losartan: _____

Candesartan: _____

Valsartan: _____

Outro: _____

Não ☐

Interrompido ☐

Beta-bloqueantes (dose):

Sim ☐

Bisoprolol: _____

Carvedilol: _____

Metoprolol: _____

Nebivolol: _____

Atenolol: _____

Não ☐

Interrompido ☐

Diurético de ansa (dose):

Sim ☐

Furosemida: _____

Não ☐

Interrompido ☐

Diurético tiazídico (dose):

Sim ☐

Hidroclorotiazida: _____

Metolazona: _____

Indapamida: _____

Clortalidona: _____

Não ☐

Interrompido ☐

Antagonista dos mineralocorticóides (dose):

Sim ☐

Espironolactona: _____

Eplerenona: _____

Não ☐

Interrompido ☐

Ivabradina (dose):	Sim ☐	Não ☐	Interrompido ☐
Digoxina (dose):	Sim ☐	Não ☐	Interrompido ☐
Dobutamina (dose):	Sim ☐	Não ☐	Interrompido ☐
Dopamina (dose):	Sim ☐	Não ☐	Interrompido ☐
Noradrenalina (dose):	Sim ☐	Não ☐	Interrompido ☐

Antiagregação plaquetar:

Aspirina 100mg Sim ☐
Não ☐
Interrompido ☐

Clopidogrel 75mg Sim ☐
Não ☐
Interrompido ☐

Ticagrelor (dose): Sim ☐
Não ☐
Interrompido ☐

Anticoagulação oral (dose): Sim ☐
Varfarina _____
Dabigatrano _____
Rivaroxabano _____
Apixabano _____
Edoxabano _____
Não ☐
Interrompido ☐

DIAGNÓSTICO DE IC NO INTERNAMENTO ACTUAL

Sim ☐

Não ☐

FÁRMACOS PARA A ALTA

IECA (dose): Sim ☐

Captopril: _____

Enalapril: _____

Lisinopril: _____

Perindopril: _____

Ramipril: _____

Trandolapril: _____

Não ☐

ARA II (dose): Sim ☐

Losartan: _____

Candesartan: _____

Valsartan: _____

Outro: _____

Não ☐

Beta-bloqueantes (dose): Sim ☐

Bisoprolol: _____

Carvedilol: _____

Metoprolol: _____

Nebivolol: _____

Atenolol: _____

Não ☐

Diurético de ansa (dose): Sim ☐

Furosemida: _____

Não ☐

Antagonista dos mineralocorticóides (dose): Sim ☐

Espironolactona: _____

Eplerenona: _____

Não ☐

Ivabradina (dose): Sim ☐ Não ☐

Digoxina (dose): Sim ☐ Não ☐

Antiagregação plaquetar:

Aspirina 100mg Sim ☐
Não ☐

Clopidogrel 75mg Sim ☐
Não ☐

Ticagrelor (dose): Sim ☐
Não ☐

Anticoagulação oral (dose):

Sim ☐
Varfarina _____
Rivaroxabano _____
Dabigatrano _____
Apixabano _____
Edoxabano _____
Não ☐

REFERENCIAÇÃO PÓS-ALTA

Cuidados Paliativos: Sim ☐
Não ☐

Follow-up Cardiologia: Sim ☐
Não ☐

Consulta de Medicina Interna: Sim ☐
Não ☐

Médico de Família: Sim ☐
Não ☐

Outras especialidades: Sim ☐
Não ☐

Data da alta: __/__/____

OUTROS

Dias de internamento por IC: último ano _____
últimos 6 meses _____
últimos 3 meses _____
último mês _____

Hospitalizações por IC: último ano _____
últimos 6 meses _____
últimos 3 meses _____
último mês _____

Síndrome Cardio-Renal tipo 1[7]: Sim ☐
Não ☐

Nota

[7] – "an increase ≥ 0.3 mg/dl in serum creatinine relative to the admission level for the purposes of the study" *in* 7th ADQI Consensus Conference.

COMPLICAÇÕES APÓS ALTA

Insuficiência Renal/Agravamento da função renal: 1 mês _____
2 meses _____
3 meses _____
6 meses _____
1 ano _____

Hospitalizações por qualquer causa (se sim diagnóstico): 1 mês _____
2 meses _____
3 meses _____

Morte por qualquer causa (se sim diagnóstico): 1 mês _____
2 meses _____
3 meses _____

Morte por IC: 1 mês _____
2 meses _____
3 meses _____